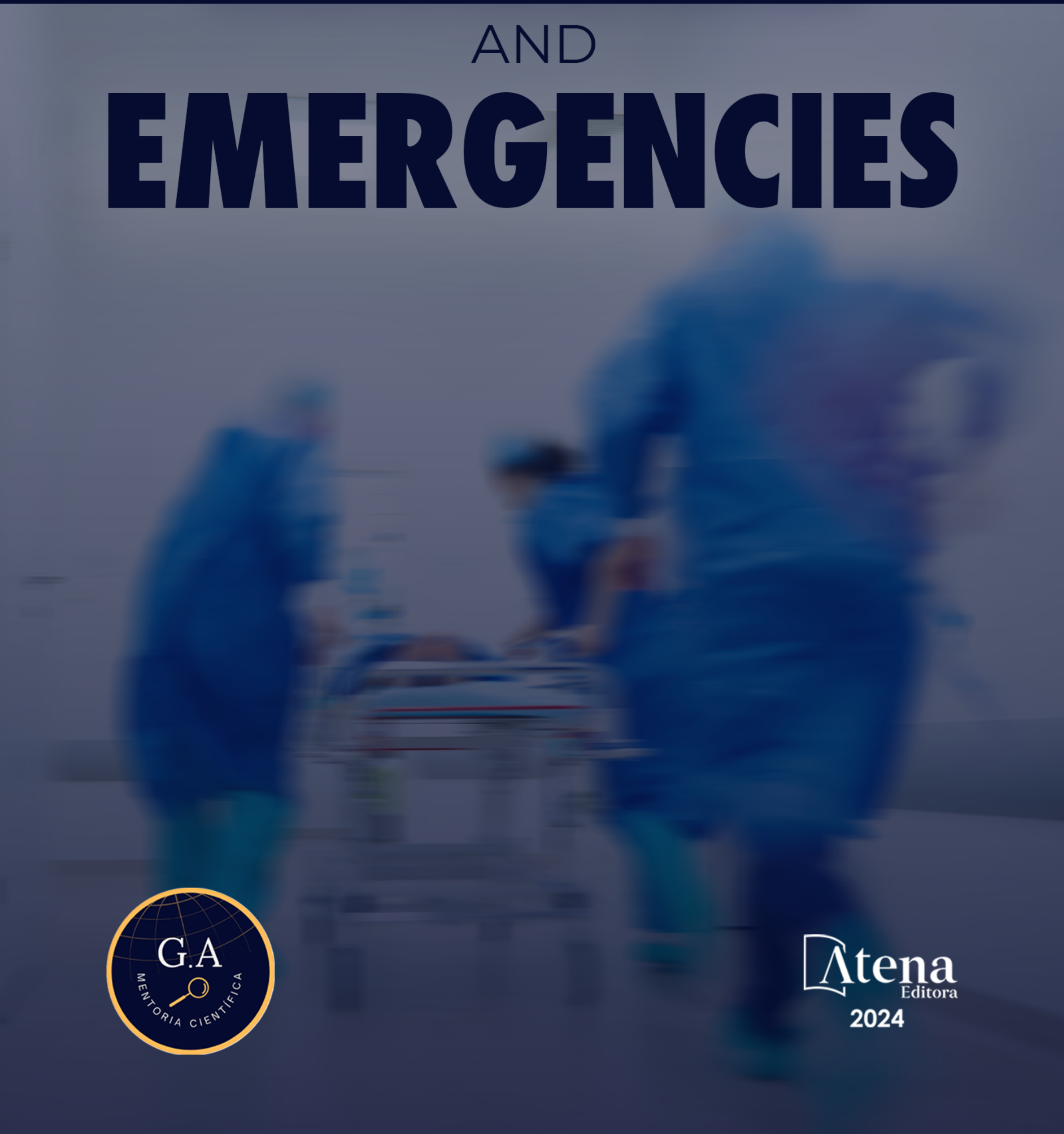
CLINICAL AND SURGICAL URGENCIES AND EMERGENCIES



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PREFACE

In the ever-evolving field of medicine, the ability to quickly and effectively manage clinical and surgical urgencies and emergencies is crucial for saving lives and improving patient outcomes. The complexity and diversity of these situations demand that healthcare professionals remain informed with the most current knowledge and best practices.

This book was conceived with the objective of providing a comprehensive, yet accessible, resource for both seasoned professionals and those still in training. Each chapter is meticulously crafted to cover essential topics in urgency and emergency care, ensuring that readers are equipped with the necessary tools to handle a wide range of critical conditions.

From the swift identification and management of acute coronary syndrome and ischemic stroke, to the life-saving interventions required in cardiorespiratory arrest in pregnant women and postpartum hemorrhage, this book addresses the scenarios that challenge even the most experienced practitioners. It also delves into the often-overlooked but equally critical areas such as psychotropic drug intoxication, suicidal behavior in the emergency room, and the management of difficult airways in traumatized patient.

In an effort to enhance understanding and application, the chapters are structured to offer both theoretical background and practical guidance. Whether it's the management of sepsis, thyrotoxic crisis, or deep vein thrombosis, the book emphasizes evidence-based approaches and highlights recent advances in the field.

We have also included chapters on more specialized topics, such as Stevens-Johnson syndrome and ocular trauma, recognizing the importance of preparedness for rare but severe conditions. The inclusion of chapters on thoracic trauma, burns, and traumatic brain injury underscores the critical need for quick, decisive action in trauma care.

Ultimately, this book aims to be more than just a reference. It is designed to be a reliable companion in the fast-paced, high-stakes environment of emergency care, where every decision counts. We hope it will serve as a valuable tool for all who dedicate themselves to the demanding and rewarding field of emergency medicine.

We would like to express our gratitude to the contributors who have generously shared their dedication and insights. Their commitment to advancing medical knowledge is evident in every page.

G.A Mentoria Científica
Thaiz Geovana Bezerra
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SUMMARY

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Chapter 1

ACUTE CORONARY SYNDROME

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CHAPTER 1

ACUTE CORONARY SYNDROME

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Acute Coronary Syndrome (ACS) refers to a set of heart conditions characterized by the obstruction of the coronary arteries, potentially leading to acute myocardial infarction. These conditions represent a group of severe clinical problems that affect millions of people worldwide. There are two types of

ischemia caused by ACS: ischemia due to elevated ST segments and ischemia caused by an excess demand for oxygen in relation to the capacity of the coronary arteries (Carey, 2016). Both types can be identified through cardiovascular exams performed in hospital emergencies. The ECG has the necessary sensitivity to detect specific markers, occurring when ischemia causes cell death in cardiac tissue, and these residues are identified through blood tests. In the context of medical urgency and emergency, ACS is one of the main causes of hospitalization and mortality in emergency services (Wang *et al.*, 2021).

ACS causes changes in specific markers on the ECG, such as elevated ST segment levels. The electrocardiogram shows these changes, and the analysis of ST segment levels is crucial for diagnosing the syndrome. Studies show that the mortality of patients with elevated ST segment levels is higher than those with low levels of this marker. Immediate treatment aims to restore blood flow to the heart. The latest trends in the diagnosis and treatment of ACS involve advanced imaging techniques, such as coronary angiography and echocardiography (ECG), in addition to thorough physical and laboratory examinations, aiming to establish an accurate differential diagnosis. Therapeutic management includes both drug therapy, with antiplatelet and anticoagulant agents, and invasive interventions, such as angioplasty and coronary artery bypass surgery (Amiri, 2019). Patients affected by ACS require continuous monitoring due to the risk of cardiac, mechanical, and thromboembolic complications (Thomas *et al.*, 2021).

Recent technological advances have improved the diagnostic and prognostic accuracy of ACS. The use of techniques such as computed tomography for coronary artery calcium assessment and carotid ultrasound for atherosclerotic plaque analysis has proven effective (Falk *et al.*, 2013). Additionally, the role of NK cells in modulating the inflammatory response and preventing cardiac fibrosis has emerged as a promising therapeutic approach (Kumrić *et all*., 2020). These advances provide a more precise and personalized approach to the treatment of cardiovascular disease. Acute Coronary Syndrome remains a significant challenge for healthcare systems due to its complexity and impact on cardiovascular morbidity and mortality. Recent advances in diagnostic and therapeutic techniques have improved clinical management and patient outcomes, promoting a more precise and personalized approach to treating this critical condition (Kumar *et al.*, 2021).

EPIDEMIOLOGY

Acute Coronary Syndrome (ACS) is the leading cause of mortality worldwide. The global incidence of ACS exceeds 20 million cases per year (Simoni *et al.*., 2023). After an ACS event, the risk of future events remains high, as patients who have had a myocardial infarction (MI) are five to six times more likely to have another MI compared to those who have never had coronary heart disease (Pottle, 2020). Despite the significant incidence of cardiovascular disease, mortality from ischemic heart disease has decreased in the general

population over the past 40 years, likely due to technological medical advancements and the refinement of major guidelines (Khraishah *et al*.., 2023). However, this reduction in mortality is more pronounced in men than in women, and the prevalence and incidence of MI in younger women (under 55 years) have increased dramatically compared to men of similar age (Khraishah *et al*.., 2023).

Studies on acute coronary syndrome (ACS) reveal significant variations in the presentation and outcomes of the disease. Men tend to manifest ACS at younger ages, while women often develop the condition post-menopause, presenting atypical symptoms that can delay diagnosis (Haider *et al*.., 2020). More developed regions generally show better survival rates, reflecting disparities in access to healthcare (Pottle, 2020). Additionally, environmental factors such as air pollution have been associated with increases in ACS incidence, more severely affecting urban populations (Mills; Pope, 2022). Elderly individuals and those with pre-existing conditions are particularly vulnerable to the adverse effects of pollution (Mills & Pope, 2022). Socioeconomic disparities also influence outcomes, with patients from lower socioeconomic classes presenting higher incidences of severe complications and worse post-event recovery (Simoni *et al*.., 2023). These demographic nuances are crucial for personalizing ACS prevention and treatment strategies, aiming to improve outcomes for all affected groups (Viana *et al*.., 2020; Zhang *et al*.., 2022).

Various factors contribute to the observed differences in mortality trends and outcomes of acute coronary syndrome (ACS) between men and women. These factors include biological aspects, variations in symptom presentation, associated comorbidities, and social and lifestyle influences. One of the most important biological factors is the difference in coronary artery size between men and women. Women have significantly smaller epicardial coronary arteries, which can affect the clinical presentation and outcomes of ACS. Additionally, dysregulation of DNA methylation (DNAm) can contribute to adverse changes in gene expression, affecting various cardiovascular risk factors, including obesity, atherosclerosis, inflammation, hypertension, dyslipidemia, and glucose metabolism. These factors collectively increase the risk of developing coronary artery disease (CAD) in women (Haider *et al*.., 2019).

The manifestation of symptoms in men and women also differs significantly. While precordial pain is the most common symptom in more than 80% of ACS cases for both sexes, women are more likely to present atypical symptoms, often attributing their symptoms to non-cardiac conditions such as esophageal acid reflux, stress, or anxiety. This difference in symptom presentation can lead to delayed or incorrect diagnosis in women, negatively affecting clinical outcomes. Young women with ACS often have a higher prevalence of comorbidities such as depression, hypertension, diabetes, and obesity compared to men of the same age group (Haider *et al*., 2019). These associated conditions can complicate the treatment and management of ACS, resulting in worse outcomes. For example, the presence of depression can influence treatment adherence and recovery after a cardiac event.

Social and lifestyle factors also play a crucial role in the differences in mortality and outcomes of ACS between men and women. Differences in access to healthcare and awareness of heart diseases can influence early detection and effective treatment of ACS. Additionally, lifestyle practices such as diet and physical activity levels can vary significantly between men and women, impacting the risk of developing CAD and other cardiovascular problems (Haider *et al.*, 2019). These biological factors, differences in symptom presentation, prevalence of comorbidities, and social and lifestyle influences combine to explain the observed differences in mortality and outcomes of ACS between men and women.

Risk factors for developing cardiovascular diseases are similar between men and women, although there are variations in the prevalence, incidence, and age of manifestation of these diseases according to sex (Haider *et al.*., 2020). Factors such as hypertension, diabetes, smoking, and high cholesterol contribute to the development of cardiovascular diseases in both sexes. However, the frequency with which these factors appear and the age at which diseases manifest can differ between the sexes.

Women with ACS are generally older and have multiple comorbidities (Haider et al., 2020). Studies suggest that women with ACS are generally 8 to 10 years older than men with the same clinical condition (Khraishah *et al.*, 2023). Additionally, women who smoke and/or have diabetes are at higher risk of ACS compared to men with the same comorbidities (Haider *et al.*, 2020). In the global case-control INTERHEART study with 27,000 individuals from 52 countries, it was observed that women with diabetes were 4.3 times more likely to suffer a myocardial infarction (MI) compared to non-diabetic women, while men with diabetes had a 2.7 times higher risk of MI compared to non-diabetic men (Khraishah *et al.*, 2023). Young women tend to have a poorer pre-event quality of life than men of the same age (Haider *et al.*, 2020). Another important finding is that younger women (under 65 years) with a maternal history of MI have a four times higher risk of ACS compared to men of the same age or older women (Haider *et al.*, 2020).

In terms of socioeconomic risks, women hospitalized for cardiovascular events tend to have greater social frailty, lower socioeconomic status, higher incidence of depression, and greater occurrence of physical problems compared to hospitalized men (Haider *et al.*, 2020). An alternative analysis notes that men and women have significant differences in gut microbiota, specifically in levels of trimethylamine N-oxide, which may contribute to survival after ACS. One study observed 30-day event-free survival for women and six-month event-free survival for men, related to the previously mentioned compound (Haider *et al.*, 2020).

Pregnancy-related complications also increase women›s cardiovascular risk. Studies show that the risk of coronary artery disease (CAD) is higher in women with a history of preeclampsia, placental abruption, gestational hypertension, and gestational diabetes (Haider *et al.*, 2020). Additionally, ethnic and racial factors also influence the risk of ACS. Generally, Black women in the United States have a higher prevalence of traditional cardiovascular disease risk factors, including diabetes, hypertension, and smoking, compared to non-Hispanic White women (Khraishah *et al.*, 2023).

Young women may be more likely to have systemic inflammatory disorders (SID), conferring a high risk of MI and cardiovascular mortality. Among 2,097 patients aged ≤ 50 years who presented with an MI episode, 53 (2.5%) had an SID diagnosis, distributed as follows: 64% psoriasis, 23% systemic lupus erythematosus, 9% rheumatoid arthritis, and 4% other SIDs (Khraishah *et al*., 2023). These varied effects of sex, age, environmental, and hereditary influences on the development of ACS highlight the condition›s complexity.

Crucial statistics on acute coronary syndrome reveal significant disparities and multiple determining factors. Women often have higher mortality rates due to less typical symptoms and underdiagnosis compared to men (Haider *et al*., 2020). Patients with cognitive impairment have higher in-hospital mortality and increased rates of cardiovascular complications, reflecting the complexity of clinical outcomes in these cases (Pottle, 2020). The adverse influence of environmental factors such as air pollution and emotional stress exacerbates the risk of severe complications and mortality among individuals with acute coronary syndrome (Mills & Pope, 2022). Socioeconomic disparities persist over time, with patients of lower socioeconomic status facing worse clinical outcomes and higher mortality, highlighting the need for interventions to reduce these inequalities (Simoni *et al*., 2023). Delays in recognizing symptoms and implementing appropriate treatments significantly contribute to high mortality rates among patients with acute coronary syndrome (Viana *et al*., 2020). Additionally, glycemic variability emerges as a significant risk factor for adverse cardiovascular events, underscoring the importance of stringent glycemic control in the effective clinical management of this condition (Zhang *et al*., 2022). These findings highlight the multifactorial complexity of ACS and emphasize the need for integrated and personalized approaches to improve clinical outcomes and reduce the mortality associated with this severe cardiovascular condition.

Over the past four decades, age-adjusted mortality for cardiovascular diseases (CVD) has steadily decreased. However, this decrease has been less pronounced in women than in men. Cardiovascular diseases remain the leading cause of morbidity and mortality in Europe, accounting for 49% of deaths in women and 40% of deaths in men (Haider *et al*., 2019). Recent studies report a significant increase in case fatality rates of acute coronary syndromes (ACS) in young women under 55, while mortality from coronary artery disease (CAD) has decreased in younger men. A recent meta-analysis concluded that the risk of CAD is higher in women with a history of preeclampsia, placental abruption, gestational hypertension, and diabetes. These trends may vary among different populations and regions due to factors such as access to healthcare, prevalence of specific risk factors, and lifestyle practices (Haider *et al*., 2019).

DIAGNOSIS

Acute coronary syndrome (ACS) has a sudden onset and rapid development, which can lead to life-threatening malignant conditions at any moment (Wang *et al.*, 2020). The morbidity and mortality of ACS compel emergency physicians to work with limited time to determine the course of action, significantly altering the disease›s progression. Rapid diagnosis is essential in any patient presenting with chest pain or anginal equivalent in the emergency room and is based on a series of findings that collectively lead to a definitive conclusion (Geyer *et al.*, 2020). The diagnosis is not always straightforward, as many patients may present with atypical symptoms and show no changes in supplementary tests.

The main complaint of a patient with ACS is unstable precordial, retrosternal, or diffuse anginal chest pain. The pain has a sudden onset, is moderate to intense, and is described as a tightness or burning sensation (Amiri, 2019). The pain may radiate to the epigastrium, upper limbs, shoulders, back, and neck, and may also cause epigastric pain, nausea, vomiting, sweating, dyspepsia, hypotension, and syncope (Amiri, 2019). The physical examination is generally nonspecific, resembling that of patients with acute myocardial infarction (AMI), and may reveal arterial hypotension (SBP < 85 mmHg), sweating and clammy skin, tachycardia (> 100 bpm), systolic murmurs of mitral origin, and pulmonary crackles (Amiri, 2019; Goldschmied *et al.*, 2024).

Chest pain is the main symptom of ischemia, but ischemia can also present as anginal equivalents: epigastric pain, dyspepsia, dyspnea, nausea and vomiting, sweating, hypotension, and syncope. Patients with acute coronary syndrome (ACS) often exhibit symptoms and signs of myocardial ischemia at rest with minimal exertion. These symptoms and signs are similar to those of chronic angina, with retrosternal chest pain that may radiate to the jaw, left shoulder, and arm. Dyspnea, nausea, sweating, and syncope may accompany chest pain or be the only acute symptoms. About one-third of AMI patients do not present with chest pain; these patients tend to be older, female, diabetic, and at higher risk of subsequent mortality. Although chest pain is the main symptom, up to 30% of patients may not experience chest pain, with elderly patients (> 75 years), women, and those with diabetes, chronic kidney disease, or dementia more commonly presenting with anginal equivalents in the emergency department with atypical complaints, including epigastric pain, dyspepsia, dyspnea, and rarely syncope. Patients may even present with generalized weakness or mental confusion. Delays in diagnosis have been well-documented and often lead to delays in therapy. Patients ≥ 75 years old have higher in-hospital mortality and are more likely to have heart failure associated with myocardial infarction, with the risk progressively increasing in each successive age group from 36% at 65-69 years old to 65% in those ≥ 85 years old (Goldschmied *et al.*, 2024).

In recent years, various innovative technologies and techniques have emerged for the diagnosis of Acute Coronary Syndrome (ACS), enhancing precision and early detection.

Laboratory diagnosis is performed using cardiac biomarkers, complete blood count, and lipid profile. Cardiac biomarkers are called myocardial necrosis markers (MNM), the main ones being troponin, myoglobin, and CK-MB. Troponin is the primary cardiac biomarker of cellular content, released after myocardial necrosis; it is a regulatory protein complex found only in the myocardium, with two main isoforms: cardiac troponin T (cTnT) and cardiac troponin I (cTnI), with cTnT being the most sensitive. After myocardial injury, serum troponin concentration begins to rise between 3-6 hours, peaking at 24 hours, and normalizing between 7-14 days (Moeckel, 2019; Wang *et al.*, 2020; Goldschmied *et al.*, 2024).

Myoglobin is another type of cellular origin cardiac biomarker used to guide the diagnosis of ACS. It is a protein involved in oxygen storage found in both muscles and myocardium, indicating injuries in striated skeletal or cardiac muscle. Its serum concentration rises earlier compared to troponin, starting 2-3 hours after injury and peaking at 8-12 hours. Its use is always associated with troponin values, as together they increase the negative predictive value of myocardial injury (Geyer *et al.*, 2020; Gajardo, Lillo-Moya, and Llancaqueo, 2024). The enzyme creatine kinase-MB (CK-MB) is an isoenzyme of creatine kinase (CK) present in striated skeletal muscle but primarily in cardiac muscle. Its serum elevation occurs 4-6 hours after myocardial injury, peaking between 12-20 hours. It is a less specific test, always requested in conjunction with troponin or in situations where troponin is unavailable (Moeckel, 2019; Geyer *et al.*, 2020).

Patients with a history of cardiovascular disease and unstable angina first exhibit increased serum concentrations of myoglobin, followed by troponin, and finally CK-MB (Moeckel, 2019; Amiri, 2019). Patients with ACS may present elevated erythrocyte sedimentation rate and leukocytosis with a left shift (Amiri, 2019). Total and fractional cholesterol and triglycerides should be collected to assess the presence of dyslipidemia, as it is a risk factor for cardiovascular diseases and a predictor of ischemia due to atheroma plaque in confirmed ACS cases (Moeckel, 2019; Amiri, 2019; Goldschmied *et al.*, 2024).

Among imaging tests, the electrocardiogram (ECG) is the initial and most important test and should be performed within 10 minutes of the admission of patients with typical ACS signs and symptoms (Moeckel, 2019). The ECG is a sensitive and specific test for detecting ischemic changes, suggesting infarctions due to complete or partial obstructions (Moeckel, 2019). The condition most closely linked to ACS is ST-segment elevation myocardial infarction (STEMI), indicating infarction due to complete myocardial obstruction (Moeckel, 2019). If the initial ECG is inconclusive, another ECG should be performed after 5-10 minutes. If the patient remains under observation, the ECG should be repeated every 3 hours for a total period of 12 hours or whenever there are changes in the patient›s clinical condition (Moeckel, 2019).

Patients with a normal ECG still have a 2% risk of presenting with ACS (Khraishah et al., 2023). Patients with nonspecific ECG changes but anginal symptoms have up to a 9% chance of having ACS (Khraishah *et al.*, 2023). Transthoracic echocardiography

(TTE) should be performed on all patients with suspected ACS as it is easy to perform, non-invasive, and has high sensitivity and specificity in identifying ventricular contractility abnormalities, ejection fraction, and mechanical complications that may be involved in the syndrome. Computed tomography angiography (CTA) is the diagnostic test of choice for assessing the extent of injury, perfusion, and prognosis in patients with ACS, especially those with non-ST-segment elevation (NSTEMI) (Kakizaki *et al.*, 2022).

To assist in the reliable diagnosis of chest pain and therapeutic strategy in the emergency setting, the HEART score was developed (Moeckel, 2019). This score estimates the probability of major cardiovascular disorders within 6 weeks in patients with suspected ACS, especially those with nonspecific chest pain and normal ECG and troponins. It is used in the emergency setting, evaluating clinical history, ECG results, age, risk factors for heart disease, and serum troponin level (Moeckel, 2019). Each variable consists of 2 points, corresponding to a maximum score of 10 points. The higher the score, the greater the suspicion of ACS, and patients should be admitted to intensive care units and monitored (Moeckel, 2019; Khraishah *et al.*, 2023).

Differentiating anginal pain is essential. Among the differential diagnoses, pulmonary thromboembolism is the main one, being a high morbidity and mortality syndrome, presenting dyspnea as the main symptom that differs from ACS, even with elevated serum troponins (Moeckel, 2019; Amiri, 2019). Acute aortic syndromes, represented by the triad of acute aortic dissection, intramural hematoma, and penetrating ulcer, have low incidence but strongly fit as differential diagnoses after excluding ACS (Moeckel, 2019; Amiri, 2019). Pericarditis is a low-prevalence condition, affecting only 5% of the general population, but it presents typical pleuritic chest pain in sharp stabs located in the anterior chest, worsening with inspiration or coughing (Moeckel, 2019; Amiri, 2019). Cardiac tamponade generates anginal pain similar to pericarditis but is strongly associated with acute conditions post-cardiological invasive procedures, such as biopsies, surgeries, pacemaker implants, angioplasty, and even AMI (Moeckel, 2019; Amiri, 2019). Pneumothorax also causes sudden chest pain, but associated with ventilatory-dependent dyspnea and worsening with exertion (Moeckel, 2019; Amiri, 2019).

Other technologies that demonstrate advances in ACS diagnosis include machine learning algorithms, which have shown great potential in predicting major adverse cardiac events (MACE) and acute coronary artery occlusion (ACAO). These algorithms outperform the accuracy of the «TropOut» score, which does not use troponin, by utilizing a wide range of clinical and pre-clinical data, quickly identifying at-risk patients even without troponin availability (Goldschmied *et al.*, 2024). Additionally, metabolomics also stands out as an innovative tool for accurate and less invasive ACS and coronary artery disease (CAD) diagnoses, using techniques such as nuclear magnetic resonance (NMR) and mass spectrometry (MS) to identify new biomarkers, improving diagnostic and prognostic accuracy (Amiri, 2019). Recently, non-coding RNAs (ncRNAs), such as microRNAs

(miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), have also emerged as promising biomarkers for ACS due to their stability in the blood, contributing to early detection, accurate diagnosis, and personalized treatment (Wang *et al.*, 2020).

Additionally, besides biomarkers, imaging tests have also advanced, such as optical coherence tomography (OCT), a high-resolution imaging technique used in the diagnosis of acute coronary syndrome (ACS) to identify three main types of atherosclerotic plaques: plaque rupture (PR), plaque erosion (PE), and calcified nodules (CN). It allows for a detailed examination of the internal structures of coronary arteries, offering an accurate diagnosis of the causes of ACS and significantly influencing the prognosis of patients. Patients with PE have better prognoses after percutaneous coronary intervention (PCI) compared to those with PR, while patients with CN have the worst clinical outcomes, including higher incidence of major adverse cardiac events (MACE) and cardiovascular mortality. OCT also allows for adjustments in PCI strategy during emergencies, improving procedural outcomes (Kondo*et al.*, 2023). Studies indicate that fractional flow reserve derived from OCT (OCT-FFR) has a robust correlation with wire-based FFR and is associated with the presence of functional ischemia. Low OCT-FFR values have been linked to target vessel failure (TVF), and its inclusion in post-PCI evaluations may improve the detection of at-risk patients, optimizing clinical outcomes (Kakizaki *et al.*, 2022).

The adoption of these new technologies and techniques has considerably improved the accuracy of diagnoses and early identification of ACS. The increased sensitivity of biomarkers allows for faster and more accurate detection of cardiac muscle injuries, while advanced imaging methods enable a detailed analysis of the heart›s structure and function (Geyer *et al.*, 2020; Moeckel, 2019; Gajardo, Lillo-Moya; Llancaqueo, 2024; Kondo *et al.*, 2023; Kakizaki *et al.*, 2022). Additionally, the use of ncRNAs as biomarkers adds a new perspective to the detection and prediction of ACS, further personalizing patient treatment and improving clinical outcomes (Wang *et al.*, 2020). In summary, recent advances in highly sensitive biomarkers, cutting-edge imaging techniques, and the discovery of non-coding RNAs have revolutionized the diagnosis of Acute Coronary Syndrome. These innovations enable a more accurate and early approach, fundamental for effective management and improved patient outcomes (Geyer *et al.*, 2020; Moeckel, 2019; Gajardo, Lillo-Moya; Llancaqueo, 2024; Kondo *et al.*, 2023; Kakizaki *et al.*, 2022; Wang *et al.*, 2020).

TREATMENT

The treatment of acute coronary syndrome (ACS) is essential and should focus on early detection, risk stratification, and immediate intervention, aiming to reduce cardiac damage, improve clinical outcomes, and prevent severe complications. ACS is one of the leading causes of cardiovascular morbidity and mortality worldwide, with increasing importance given the aging population (Crea;Libby, 2017). Following the diagnosis of ACS, the initial

therapeutic approach includes supportive measures, antithrombotic and anticoagulant drug therapy, and invasive or conservative reperfusion strategies. Patients with ACS require early risk stratification to guide the search for the best intervention, considering their needs. Therapeutic adjustments also need to be made, as despite inflammation playing the main role in the pathophysiology of ACS, other underlying mechanisms need to be considered: plaque rupture with systemic inflammation, plaque rupture without systemic inflammation, plaque erosion, and plaque without thrombus; allowing for the implementation of precise and personalized therapeutic approaches according to the etiology (Crea ; Libby, 2017).

Historically, aspirin has been the first-line antithrombotic treatment in cardiovascular diseases. Subsequently, new antiplatelet agents, including P2Y12 inhibitors, were evaluated in addition to aspirin. The choice of the optimal antiplatelet strategy after ACS or PCI at the individual level is a conundrum that requires stratification of ischemic and hemorrhagic risks (Guedeney *et al.*, 2020). Among conventional pharmacological treatments, antiplatelet agents, especially P2Y12 receptor inhibitors (clopidogrel, prasugrel, and ticagrelor), stand out for preventing platelet aggregation and suppressing systemic inflammation (Thomas *et al.*, 2021).

Large randomized clinical trials and recent meta-analyses have demonstrated that dual therapy based on a non-vitamin K oral anticoagulant and a P2Y12 inhibitor is superior to triple therapy based on a vitamin K antagonist with dual antiplatelet therapy (DAPT) for preventing bleeding. However, several of these trials also reported an increase, although not significant, in coronary ischemic events in case of aspirin discontinuation (Guedeney *et al.*, 2020). In a recent study, clopidogrel and ticagrelor were predominantly used as P2Y12 inhibitors based on single antiplatelet therapy. Given the significant proportion of patients with an inadequate response to clopidogrel therapy, as detected by platelet function or genetic tests, concerns have arisen regarding its use as single antiplatelet therapy, particularly in patients without a history of oral anticoagulants (OAC) (Guedeney *et al.*, 2020). In a retrospective study based on the Israeli Acute Coronary Syndrome Survey (ACSIS) registry, patients after ACS present a particularly increased risk of recurrent cardiovascular events (Grinberg *et al.*, 2022). However, strategies based on P2Y12 inhibitors› genotype or platelet function testing did not result in a significant reduction of ischemic complications in dedicated trials, suggesting that clopidogrel alone can be safely used in these patients. Consistently, no significant interaction was found between the effect of early aspirin discontinuation and prolonged single antiplatelet therapy with clopidogrel or ticagrelor in patients who do not require chronic OAC (Guedeney *et al.*, 2020).

The results of early aspirin discontinuation on safety and efficacy events remained consistent according to the type of P2Y12 inhibitors predominantly used (i.e., clopidogrel vs. ticagrelor). Furthermore, the optimal timing for aspirin discontinuation remains unclear. In all trials with patients presenting an underlying indication for chronic OAC, aspirin use was allowed during Percutaneous Coronary Intervention (PCI) and before randomization, which

generally occurs between four hours after the arterial sheath removal and up to 14 days after PCI/ACS. On the other hand, in studies including patients without an indication for chronic OAC, aspirin discontinuations occurred one month or three months after randomization (weighted mean DAPT duration of 1.7 months). Notably, no significant interaction was found in the effect of aspirin discontinuation between one month and three months (Guedeney *et al.*, 2020).

In ACS caused by plaque rupture with inflammation, colchicine, an antirheumatic drug, was able to reduce cardiovascular events in a medium-sized open-label randomized study (Crea; Libby, 2017). Colchicine›s mechanism of action is related to the activation of the NLRP3 inflammasome, resulting in a reduction of interleukin IL-1β and interleukin 18 (Wang et al., 2020). A large phase III study (n>10,000) determined a 15% reduction in the primary endpoint of myocardial infarction and a 30% reduction in revascularization procedures in the group that received canakinumab, an anti-IL-1β monoclonal antibody, every three months in patients with a history of MI and CRP > 2mg/L, reinforcing the contribution of inflammation to the atherosclerotic process (Crea; Libby, 2017).

IL-1β inhibition with canakinumab has shown success in treating residual inflammatory risk (RIR) in coronary arteries, raising the potential implication of anti-inflammatory therapy in ACS patients. Reducing inflammation through cytokine inhibition such as IL-1β may help stabilize atherosclerotic plaques and reduce the risk of acute cardiovascular events. This therapeutic approach represents a new perspective in treating ACS, focusing not only on reducing cholesterol but also on modulating the inflammatory response (Wang *et al.*., 2020).

Studies indicate that the use of anacetrapib, a potent inhibitor of cholesterol ester transfer protein (CETP), in ACS due to plaque rupture without inflammation, not only increases high-density lipoprotein (HDL) but also reduces low-density lipoprotein (LDL). However, more studies are needed to attribute event reduction to HDL increase, possibly associated with atherosclerotic plaque stabilization. Statins and ezetimibe can also reduce cholesterol crystal formation. Cyclodextrin has been used to combat cholesterol crystal accumulation by solubilizing them (Crea; Libby, 2017).

Currently, the treatment of epicardial spasm, the main contributor to atherosclerotic plaque instability in ACS patients without thrombus in plaques, uses long-acting nitrates and calcium channel blockers. However, many patients do not respond to these vasodilators. Understanding post-receptor mechanisms responsible for nervous system hyperreactivity and epicardial spasm is necessary to create new therapeutic alternatives (Crea; Libby, 2017).

Immunological and inflammatory dysfunctions have been associated with the pathogenesis of acute coronary syndrome. Studies show that inflammation plays an important role in the development and progression of cardiovascular diseases, including acute coronary syndrome. The activation of the immune system and the inflammatory response can contribute to the formation of atherosclerotic plaques and the instability of

these plaques, leading to acute events such as myocardial infarction. It is important to consider these aspects in the treatment and prevention of acute coronary syndrome (Wang *et al.*, 2020).

REFERENCES

AMIRI, Mohammad Pouralijan et al. Metabolomics in early detection and prognosis of acute coronary syndrome. **Clinica Chimica Acta**, v. 495, p. 43-53, 2019.

CAREY, Mary G. Acute coronary syndrome and ST segment monitoring. **Critical Care Nursing Clinics**, v. 28, n. 3, p. 347-355, 2016.

CREA, Filippo; LIBBY, Peter. Acute coronary syndromes: the way forward from mechanisms to precision treatment. **Circulation**, v. 136, n. 12, p. 1155-1166, 2017.

FALK, Erling et al. Update on acute coronary syndromes: the pathologists› view. **European heart journal**, v. 34, n. 10, p. 719-728, 2013.

GAJARDO, Abraham IJ; LILLO-MOYA, José; LLANCAQUEO, Marcelo. Navigating beyond numbers: the clinical context and the role of high-sensitivity troponin on long-term outcomes of patients with suspected acute coronary syndrome. **European Journal of Preventive Cardiology**, p. zwae067, 2024.

GEYER, Martin et al. State of the Art—High-Sensitivity Troponins in Acute Coronary Syndromes. **Cardiology Clinics**, v. 38, n. 4, p. 471-479, 2020.

GOLDSCHMIED, Andreas et al. Preclinical identification of acute coronary syndrome without high sensitivity troponin assays using machine learning algorithms. **Scientific Reports**, v. 14, n. 1, p. 9796, 2024.

GRINBERG, Tzlil et al. Management and outcomes over time of acute coronary syndrome patients at particularly high cardiovascular risk: the ACSIS registry-based retrospective study. **BMJ open**, v. 12, n. 4, p. e060953, 2022.

GUEDENEY, Paul et al. Early aspirin discontinuation following acute coronary syndrome or percutaneous coronary intervention: a systematic review and meta-analysis of randomized controlled trials. **Journal of Clinical Medicine**, v. 9, n. 3, p. 680, 2020.

HAIDER, Ahmed et al. Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome. **European heart journal**, v. 41, n. 13, p. 1328-1336, 2020.

KAKIZAKI, Shunsuke et al. Optical coherence tomography fractional flow reserve and cardiovascular outcomes in patients with acute coronary syndrome. **Cardiovascular Interventions**, v. 15, n. 20, p. 2035-2048, 2022.

KHRAISHAH, Haitham et al. Sex, racial, and ethnic disparities in acute coronary syndrome: novel risk factors and recommendations for earlier diagnosis to improve outcomes. **Arteriosclerosis, thrombosis, and vascular biology**, v. 43, n. 8, p. 1369-1383, 2023.

KONDO, Seita et al. Diagnosis and Prognostic Value of the Underlying Cause of Acute Coronary Syndrome in Optical Coherence Tomography–Guided Emergency Percutaneous Coronary Intervention. **Journal of the American Heart Association**, v. 12, n. 20, p. e030412, 2023.

KUMAR, Rajesh et al. Prospective validation of heart score for suspected acute coronary syndrome patients. **J Ayub Med Coll Abbottabad**, v. 34, n. 3, p. 452-7, 2021.

KUMRIĆ, Marko et al. The role of natural killer (NK) cells in acute coronary syndrome: A comprehensive review. **Biomolecules,** v. 10, n. 11, p. 1514, 2020.

MILLS, Nicholas L.; POPE, C. Arden. Environmental Triggers of Acute Coronary Syndromes. **Circulation**, v. 145, n. 24, p. 1761-1763, 2022.

MOECKEL, Martin. Biomarkers in the diagnosis of cardiovascular emergencies: Acute coronary syndrome and differential diagnoses. **Der Internist**, v. 60, p. 564-570, 2019.

POTTLE, Alison. Prevalence and patterns of cognitive impairment in acute coronary syndrome patients: A systematic review. **European Journal of Preventive Cardiology**, v. 27, n. 3, p. 281-283, 2020.

SIMONI, Amalie H. et al. Temporal trends in socioeconomic disparity in clinical outcomes for patients with acute coronary syndrome. **Cardiovascular Revascularization Medicine**, v. 56, p. 64-72, 2023.

THOMAS, Mark R. et al. Prognostic impact of baseline inflammatory markers in patients with acute coronary syndromes treated with ticagrelor and clopidogrel. **European Heart Journal Acute Cardiovascular Care**, v. 10, n. 2, p. 153-163, 2021.

VIANA, Marta et al. Patient and system delays in the treatment of acute coronary syndrome. **Revista portuguesa de cardiologia**, v. 39, n. 3, p. 123-131, 2020.

WANG, Aqian et al. Prognostic implications of ST-segment elevation in lead aVR in patients with acute coronary syndrome: a meta-analysis. **Annals of Noninvasive Electrocardiology**, v. 26, n. 1, p. e12811, 2021.

WANG, Haiming et al. Immune and inflammation in acute coronary syndrome: molecular mechanisms and therapeutic implications. **Journal of Immunology Research**, v. 2020, p. 1-11, 2020.

WANG, Lijie et al. Noncoding RNAs as biomarkers for acute coronary syndrome. **BioMed Research International,** v. 2020, 2020.

ZHANG, Lei et al. Glycaemic variability and risk of adverse cardiovascular events in acute coronary syndrome. **Diabetes and Vascular Disease Research**, v. 19, n. 6, p. 14791641221137736, 2022.

Chapter 2

ISCHEMIC STROKE

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CHAPTER 2

ISCHEMIC STROKE

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Ischemic Stroke (IS) is a severe medical condition resulting from the interruption of blood supply to a part of the brain, leading to brain tissue injury. This event is triggered by various mechanisms,

including oxidative stress, acidosis, excitotoxicity, calcium overload, mitochondrial dysfunction, inflammation, and programmed cell death. Additionally, recent studies have shown that autophagy may be related to the development of the condition. The initial interruption results in a reversible loss of neuronal function, followed by irreversible damage if blood flow is not quickly restored. The acute nature of IS requires an urgent medical response to minimize brain damage and improve clinical outcomes for patients (Feske, 2021; Wang *et al.*, 2021).

Stroke is one of the leading causes of mortality, severe disability, and hospitalization due to neurological diseases worldwide. Responsible for approximately 9% of all global deaths, stroke is a critical case in the field of Clinical and Surgical Emergencies. Although preventing strokes is the most effective strategy to reduce their occurrence and improve patient health, the time window between the onset of symptoms and irreversible tissue injury is crucial. This interval, which can range from minutes to many hours, offers a vital opportunity for urgent interventions that can restore blood flow. This condition underscores the fundamental importance of rapid action and understanding the underlying mechanisms of stroke to develop effective therapies (Feske, 2021; Wang *et al.*, 2021).

IS accounts for 60-80% of all strokes. In the United States, the prevalence of stroke in 2016 was 2.5%, with nearly 800,000 events and 150,000 deaths. Important risk factors include advanced age, female sex, ethnicity, diabetes mellitus, hyperlipidemia, smoking, and cardiovascular diseases. In addition to genetic factors, moderate alcohol consumption and regular physical activity have been found to have protective effects against stroke. Acting on the prevention of these risk factors has led to a decrease in stroke incidence since 1999. However, the risk has increased over the years due to population aging. Furthermore, the importance of continuous advancements in emergency techniques, which have revolutionized the treatment of acute IS, is highlighted to optimize patient health outcomes (Feske, 2021; Wang *et al.*, 2021).

For an immediate diagnosis, brain imaging is used, i.e., imaging diagnosis is performed. Through non-contrast cranial computed tomography (CT), the presence of hemorrhage, which may appear as hyperdensity, is verified. In CT, it is essential to observe the following points: presence of hemorrhage or other diagnoses, signs of infarction, and identification of the location of vascular injury. When the stroke is recent, the cranial CT result usually does not show hemorrhage, making it possible to perform magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA) (Feske, 2021; Wang *et al.*, 2021).

The autophagy process is the body›s response to stroke, alleviating cellular stress by removing damaged organelles. However, it is not sufficient to contain the damage caused by the stroke. Thus, therapeutic manipulation is necessary and is related to early reperfusion of the at-risk tissue with intravenous thrombolysis and/or endovascular thrombectomy and optimization of the hemodynamic state through the management of fluid volume, blood pressure, and cardiovascular status. The use of anticoagulants is also pertinent in the

treatment as a way to prevent a second stroke. Warfarin is an example of a well-known anticoagulant medication used to prevent venous thrombosis and blood clots (Feske, 2021; Wang *et al.*, 2021).

It is worth noting that current trends in stroke management aim to use advanced neuroimaging, which allows for faster diagnosis crucial for immediate intervention. One of the innovative treatments used is the use of thrombolytic drugs to dissolve cerebral clots, allowing blood flow to be quickly restored and minimizing permanent damage. Emphasis on early rehabilitation, including physical therapy, speech therapy, and occupational therapy, is increasing. This integrated approach helps in the recovery of motor, linguistic, and cognitive functions, improving the quality of life and functional outcomes for patients. Regarding prevention and education, it is vital to raise public awareness about the signs of stroke and the importance of rapid intervention. Prevention also involves strict control of risk factors such as hypertension, diabetes, and unhealthy lifestyle habits (Pinto *et al.*, 2023).

EPIDEMIOLOGY

Stroke is the second leading cause of death and the third most common cause of disability worldwide (Feske, 2021). It is a multifactorial disease influenced by genetic, epigenetic, and environmental factors (Jia *et al.*, 2022). About 85% of strokes are ischemic, and 15% are hemorrhagic. Occlusion of the middle cerebral artery leads to damage to the brain parenchyma and a neuroinflammatory response caused by the interruption of cerebral blood flow, potentially resulting in permanent neurological deficits, dementia, or death (Feske, 2021).

Among the pathology›s risk factors, 90% of stroke cases are associated with behavioral factors (poor nutrition, low physical activity, smoking) and metabolic factors (diabetes, obesity, hyperglycemia, hypertension). Additionally, the aging population increases the negative influence of stroke (Feske, 2021). Studies indicate that 15-18% of ischemic strokes (IS) occur in young adults, a number equivalent to 7 per 100,000 inhabitants. It is suggested that the causes of IS in young people differ from those in the older population, but few studies elucidate these differences. However, it is important to emphasize that the impact on the quality of life of younger IS patients is more severe, as they will have to live with the condition for a longer period. An observational study in a hospital in Fukuoka, Japan, conducted with 15,860 patients aged 18 to 50 years, suggested that the history of IS and hemorrhagic stroke (HS) was defined as one of the main risk factors, as well as hypertension, diabetes mellitus, dyslipidemia, alcohol consumption, smoking, and obesity (Lee; Mohd Ismail and Wei, 2021).

Regarding stroke risk factors, it is worth emphasizing metabolic causes, such as Diabetes Mellitus (DM), which generates the production of reactive oxygen species and inflammatory processes, mechanisms that accelerate atherosclerosis and increase

thrombus formation, leading to ischemic stroke. DM is a chronic disease characterized by hyperglycemia and affects 537 million adults globally, with a prevalence of 10.5% among adults aged 20 to 79 years. Among IS and HS patients, 33% and 26% are diabetic, respectively. A meta-analysis of 102 studies showed that diabetes doubles the risk of stroke recurrence and increases the likelihood of death, disability, cognitive impairment, and dementia after an ischemic stroke (Wang *et al*., 2021).

It is noteworthy that there is a relationship between cerebral ischemia, immune cells, intracranial atherosclerosis, and gut microbiota. Gut microbiota can be a risk factor and influence the prognosis after a stroke. The brain and intestine are connected by a neuronal network, forming a gut-brain axis with bilateral interactions. Post-stroke intestinal dysbiosis is common and can affect the production of short-chain fatty acids, such as butyrate, which has anti-inflammatory functions and is essential for maintaining intestinal barrier integrity and inhibiting pro-inflammatory cytokines. Up to 50% of post-stroke patients have gastrointestinal complications, such as constipation, dysphagia, bleeding, and fecal incontinence, negatively affecting treatment outcomes, increasing mortality, and neurological deficits. Studies indicate that the removal of gut bacteria worsens the post-stroke prognosis, while the composition of cecal microbiota changes after focal cerebral ischemia. High levels of Trimethylamine N-oxide (TMAO) are associated with poor treatment outcomes in ischemic brain injuries and increased risk of thrombosis. Modifying TMAO levels could be a promising therapeutic approach. Thus, gut microbiota plays a crucial role in stroke development and treatment, and chronic systemic inflammation post-stroke may be an important therapeutic target to improve clinical outcomes (Feske, 2021).

As mentioned above, stroke is also influenced by epigenetic factors, which can be hereditary but also undergo changes during life in response to lifestyle and environmental exposure. Epigenetic mechanisms include DNA methylation, post-transcriptional histone modifications, changes in chromatin and nucleosome. Some of these processes, such as DNA methylation and post-transcriptional histone modifications, play a crucial role in cellular response and recovery after stroke, as these mechanisms affect chromatin structure and gene transcription, promoting tissue repair and reorganization of damaged tissue cells, influencing neural recovery. DNA methylation, performed by DNA methyltransferase (DNMT), is regulated by factors such as diet, gender, race, and inflammation, which can influence gene expression and is associated with genomic instability and stroke development risk. It is noteworthy that methylation varies throughout life and tends to decrease with age, reflecting environmental risk factors related to aging. Histone modifications such as acetylation and deacetylation are typically physiologically regulated by histone acetylases (HAT) and histone deacetylases (HDAC), respectively. However, in stroke, these alterations have a disturbed balance. Deacetylation and acetylation can generate abnormal histone modifications, leading to smooth muscle cell proliferation, contributing to stroke risk. Non-coding RNAs (ncRNAs) also regulate gene expression and chromatin structure. Subclasses

of ncRNAs, such as tRNA, rRNA, miRNA, snRNA, and lncRNA, are involved in DNA methylation, acetylation, transcriptional and translational regulation, alternative splicing, post-transcriptional modification, and chromatin structure alteration. Enzyme complexes, chromatin modifications, and hypomethylation of long interspersed nuclear element-1 (LINE-1) are associated with a higher risk of stroke due to changes in lipid profiles and atherosclerotic plaque formation. Hyperhomocysteinemia is also a risk factor for stroke and atherosclerosis and occurs when the CBS enzyme is silenced by hypermethylation, preventing homocysteine from being metabolized into cysteine, resulting in high levels of homocysteine, which in turn cause hypomethylation and increased stroke risk. These epigenetic modifications are reversible, offering potential biomarkers for diagnosis and new therapeutic targets. Studies show that epigenetic interventions, such as DNA methyltransferase (DNMT) and histone deacetylase (HDAC) inhibitors, can reduce ischemic injuries and promote tissue recovery. RNA-based therapies and DNMT and HDAC inhibitors are being investigated as promising therapeutic options for stroke treatment (Jia *et al.*, 2022).

An important variable to highlight in the epidemiology of Ischemic Stroke (IS) is the circadian moment data at stroke onset. Studies indicate that the progression of Stroke varies according to the circadian cycle, which influences its severity, progression, and long-term outcomes. The study involved 17,461 consecutive patients with witnessed ischemic stroke within 6 hours of onset. The time of stroke onset was divided into two groups (daytime onset [06:00 to 18:00] versus nighttime onset [18:00 to 06:00]) in 4-hour intervals. Preclinical data indicate that stroke initiated during the inactive phase (nighttime for humans) results in greater cell death and infarct growth. In other words, it has greater initial neurological severity, worse functional outcomes at 3 months, and a higher likelihood of early neurological deterioration (END), defined as any new or worsening neurological signs or symptoms within 72 hours after stroke onset. The study›s analysis revealed that nighttime strokes were more frequent among males, young people, and smokers, with a lower prevalence of hypertension. Patients with stroke onset between 18:00 and 02:00 had a higher risk of END.

DIAGNOSIS

Recent studies have highlighted that early identification, emergent intervention, and treatment are factors that can substantially decrease stroke-related fatalities. In cases of ischemic stroke, treatment efficacy depends on early identification followed by immediate administration of reperfusion methods. Early detection includes predicting the likelihood of occurrence based on the extent of risk factors and diagnosing at an early stage with subtle symptoms (Yang *et al.*, 2024).

Each year, there are about 12 million new ischemic stroke patients worldwide. This condition is a significant burden on society due to its high incidence, mortality, and sequelae

rates. Therefore, effective diagnosis and treatment are indispensable. Currently, the primary method for diagnosing ischemic stroke is through brain imaging tests, which show the location and extent of brain injury and help distinguish between ischemic and hemorrhagic stroke (Gao *et al.*, 2024).

The most common imaging tests are computed tomography (CT) and magnetic resonance imaging (MRI). CT is more common and readily available, offering advantages such as speed, ease of use, and low cost. Additionally, CT can rule out hemorrhagic stroke and detect other diagnoses with stroke-like symptoms. However, its disadvantages are related to low sensitivity and specificity for early-stage ischemic stroke, along with patient exposure to radiation. MRI is more advanced and detailed for ischemic stroke, with high sensitivity and specificity for ischemic etiology, capable of showing small and deep lesions unlike CT. Moreover, MRI provides information such as the age, size, and type of stroke and the area of potentially salvageable brain tissue. Its disadvantages are high cost, longer execution time, and less availability, with potential contraindications such as patients with metallic implants, pacemakers, or claustrophobia. These imaging tests are expensive and require extensive equipment for large hospitals. Despite excellent diagnostic results in revealing the ischemic area, they do not offer information on disease progression or patient prognosis (Gao *et al.*., 2024).

Thus, identifying body fluids with biomarkers that are easily measured and highly specific and sensitive can address this issue. In a study by Tao et al., low expression levels of MRPS11 and MRPS12 were found in the peripheral blood of ischemic stroke patients, suggesting that MRPS11 and MRPS12 could be biomarkers for this etiology. Additionally, elevated concentrations of neurofilament light chain (NFL) and glial fibrillary acidic protein (GFAP) were found in the serum of ischemic stroke patients, indicating that NFL and GFAP could also serve as biomarkers. However, further studies on biomarkers are still needed (Gao *et al.*, 2024).

Typical symptoms of a stroke include sudden severe headache; unilateral weakness, numbness, or paralysis of the face, arms, or legs; blindness or double vision in one or both eyes; slurred, incoherent, or difficult-to-understand speech; loss of balance or coordination; and vertigo (Gao *et al.*., 2024).

In addition to common etiology symptoms, symptom variation may occur due to monogenic disorders, which are specific genetic alterations following a Mendelian inheritance pattern and can lead to stroke. Monogenic ischemic strokes occur in only 7% of patients, but it is necessary to know and diagnose the most common syndromes (Ekkert *et al.*, 2021).

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is the most common cause of monogenic ischemic stroke. Clinical symptoms include recurrent strokes in young or middle-aged adults, migraine with aura, progressive dementia, apathy, and psychiatric disorders of small cerebral vessels.

Other manifestations of this disease include premature alopecia (about 90%), early vascular dementia, and severe back pain with lumbar disc herniation (Ekkert *et al.*, 2021).

Fabry Disease, caused by a mutation in the GLA gene, manifests in early age, causing neuropathies and acroparesthesias. Other symptoms include chronic abdominal pain, angiokeratoma, renal dysfunction, cardiac arrhythmias, and hypertrophy. Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS) differ from the cited disorders as it is caused by a mitochondrial DNA (mtDNA) variant inherited from the mother. Typical symptoms include seizures, migraine-type headache, ataxia, hearing impairment, diabetes, muscle weakness, and myopathy. Retinal Vasculopathy with Cerebral Leukodystrophy (RVCL) is an autosomal dominant disease caused by a mutation in the TREX1 gene. RVCL affects small vessels, causing progressive vision loss, migraine, psychiatric abnormalities, cognitive impairment, seizures, and ischemic strokes (Ekkert *et al.*, 2021).

Other similar but clinically different conditions include Vascular Ehlers-Danlos Syndrome, manifesting with vascular, urinary, intestinal, and reproductive system fragility, and Sickle Cell Disease, an autosomal recessive disease caused by a mutation in the β-globin subunit (HBB), characterized by acute pain crises, chest syndrome, stroke, and other chronic complications. Homocystinuria, caused by a mutation in the cystathionine β-synthase gene, is characterized by corresponding enzyme deficiency, presenting clinical manifestations involving retinal, skeletal, vascular, and neurological pathology (Ekkert *et al.*, 2021).

To diagnose ischemic stroke (IS), various diagnostic methods are used, including physical, laboratory, and imaging tests. In the physical exam, the physician conducts a detailed neurological assessment, which involves reflex tests, muscle strength evaluation, coordination, sensitivity, and visual function. Additionally, the patient›s medical history is crucial to identify risk factors such as hypertension, diabetes mellitus, smoking, and a family history of vascular diseases, which may contribute to the development of IS.

In laboratory tests, a complete blood count is performed to detect possible abnormalities in blood cells, a lipid profile to assess cholesterol and triglyceride levels, and blood glucose levels to identify diabetes. Coagulation testing is essential to evaluate blood clotting capacity, providing important information about the risk of clot formation that can lead to IS. Among imaging tests, CT and MRI stand out. CT is used to visualize the brain and identify areas of ischemia or hemorrhage, while MRI provides detailed images that allow identification of small ischemic areas and assessment of the extent of brain damage. Carotid artery Doppler ultrasound complements the diagnosis by evaluating blood flow in the carotid arteries, identifying obstructions that may predispose to IS. Cerebral angiography allows direct visualization of cerebral arteries, enabling identification of areas of narrowing or occlusion that may cause or contribute to IS (Yang *et al.*., 2021; Gao *et al.*., 2024).

Beyond these conventional methods, radiomics is emerging as a promising technique. Recent studies have explored radiomics for advanced analysis of medical

images. Radiomics is a rapidly developing research field focusing on extracting measurable metrics, called radiomic features, from medical images. These features represent tissue and pathological attributes, such as heterogeneity and shape, and can be effectively used together. Compared to traditional clinical radiographic assessments, radiographic imaging offers benefits such as non-invasiveness, non-destructiveness, cost-effectiveness, rapid analysis, and easy serialization. Radiomics involves several steps. Initially, radiologists and specialists delineate regions of interest in medical images. Next, radiomic features are derived from these regions, encompassing characteristics such as intensity, shape, and texture. The most significant features are then selected to build the foundational model. The growing adoption of radiomics is mainly due to its remarkable compatibility with artificial intelligence, simplifying automated image segmentation and result production. This integration aids healthcare professionals in quick and accurate diagnosis and other clinical assessments (Yang *et al.*, 2024; Steliga *et al.*, 2020).

This approach allows extraction of quantitative and qualitative information from CT and MRI images, identifying subtle and complex patterns that may not be evident in traditional visual analysis. The application of radiomics in IS diagnosis can significantly improve diagnostic and prognostic accuracy, aiding in the selection of the best therapeutic strategies and predicting patient clinical outcomes (Yang *et al.*, 2021; Gao *et al.*., 2024).

However, it is essential to consider the need for standardization of imaging protocols and overcoming technical challenges to ensure the reproducibility and reliability of results in different clinical and research scenarios.

The differential diagnosis of IS is crucial to distinguish this condition from other conditions with similar symptoms. One of the main challenges is to differentiate IS from conditions such as Transient Ischemic Attack (TIA), where brief episodes of neurological dysfunction occur without permanent infarction, usually resolving within 24 hours and without leaving visible damage on imaging tests. Additionally, migraine with aura can present temporary neurological symptoms followed by characteristic headache, distinguished by a history of migraines and the absence of ischemia signs on imaging tests. Other conditions to consider in the differential diagnosis include hypoglycemia, which can mimic neurological symptoms due to low blood glucose levels, quickly confirmed by glucose measurement. Seizures, in turn, can manifest focal symptoms similar to IS, with differentiation aided by EEG and a history of epilepsy. Brain tumors, by compressing brain structures, can cause progressive neurological symptoms identified by imaging tests such as CT and MRI. Finally, multiple sclerosis, characterized by variable symptoms related to demyelinating lesions in the central nervous system, requires a combined analysis of clinical history, imaging tests, and cerebrospinal fluid analysis for proper differential diagnosis (Yang *et al.*., 2021; Gao *et al.*., 2024)..

A systematic review examined cerebrospinal fluid biomarkers for the diagnosis and prognosis of acute ischemic stroke, highlighting the importance of distinguishing this

condition from other conditions with similar symptoms. The discussion emphasizes the need for specific criteria to differentiate between different types of stroke and other neurovascular pathologies. Biomarkers such as specific proteins, neurofilaments, and inflammatory markers have shown significant potential in accurately differentiating between ischemic and hemorrhagic stroke, as well as other neurological conditions that may present similar symptoms. Incorporating these biomarkers into diagnostic protocols not only facilitates early and accurate diagnosis but also allows risk stratification and selection of more appropriate therapies for each patient, representing a promising research area to enhance clinical care and improve patient outcomes (Naik *et al.*, 2021).

The inability to accurately diagnose a patient in the early phase of ischemic stroke can affect up to 30% of cases. The use of diagnostic tests based on biomarker panels is rationally justified in cases of: lack of characteristic symptoms, initial assessment by non-specialists, normality in conventional imaging exams, inaccessibility of equipment such as MRI or angiography, and cases where disease characterization is incomplete (absence of patient history, unknown onset of symptoms, incomplete clinical examination). Therefore, there is a gap for the introduction of simple, inexpensive, and reliable diagnostic methods, including those based on the use of biomarkers (Steliga *et al.*, 2020). Rapid and economically accessible molecular biomarkers have proven indispensable in managing specific pathologies. Identifying biomarkers for the accurate diagnosis of ongoing or imminent cerebral ischemia and for predicting clinical outcomes represents a significant shift in clinical decision-making (Niak *et al.*, 2023).

The gold standard and the goal in the search for the ideal biomarker for ischemic stroke involve a sensitive, measurable substance that is objectively evaluated as an indicator of specific physiological and pathological processes associated with a particular type of stroke. This biomarker should show an increase in concentration during a defined period after symptom onset, reflecting responses to therapeutic interventions. The biomarker›s utility also depends on its availability for diagnostic purposes, which is related to its presence in physiological fluids such as blood or cerebrospinal fluid (CSF). Due to the CSF›s proximity to the microenvironment of acute ischemic stroke, biomarkers collected from CSF may offer greater sensitivity compared to other diagnostic tools, thus providing more reliable and early identification (Steliga *et al.*, 2020).

Three of the most frequently used CSF markers are S100beta (S100B), a specific indicator produced by astrocytes that envelop blood vessels in the brain, and the two inflammatory markers interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α). Another commonly cited factor is free fatty acids, a measure of lipid and cell degradation. Other biomarkers have diagnostic importance in different phases of ischemic stroke, such as Glial Fibrillary Acidic Protein (GFAP) and Neuron-Specific Enolase (NSE) (Steliga *et al.*, 2020).

S100β is present in astrocytes, oligodendrocytes, and Schwann cells and acts as a marker of neuroprotective or neurotoxic function. Elevated concentrations of S100β promote

necrotic and apoptotic cell death. It can be used to assess malignant and hemorrhagic stroke transformation and to exclude stroke mimics. There is a correlation between serum levels of S100β and levels in CSF, as well as infarct volume. S100β leakage from astrocytes begins about 4 hours after ischemia onset and depends on reduced cerebral blood flow and tissue destruction. S100β levels in CSF are positively correlated with stroke severity. Additionally, S100β undergoes early upregulation in the course of brain tissue damage and is a good predictor of injurious events. Increased S100β concentration can provide an early warning signal before it becomes visible on CT imaging in the early phase of stroke. This biomarker can be useful for predicting the development of malignant stroke, increased infarct volume, or excluding stroke mimics (Steliga *et al.*, 2020; Niak *et al.*, 2023).

IL-6 is a pro-inflammatory cytokine secreted by microglia or astrocytes, depending on whether it is the acute or subacute phase of ischemic stroke, respectively. Its serum levels increase during ischemic stroke and can be used as a predictor of stroke prognosis along with assessing infarct extent. Elevated IL-6 concentrations after 6 hours and increased NIHSS scores on admission promote early deterioration within 48 hours or death up to 72 hours after ischemic infarction onset. IL-6 concentration also correlates with S100β levels and the extent of tissue damage. Changes in serum IL-6 concentration are not exclusive to ischemic strokes and have also been observed during subarachnoid hemorrhage and hemorrhagic stroke. In severe strokes (NIHSS 21-42), IL-6 levels are elevated and persist in chronic changes (>1 week) after stroke. Additionally, TNF-α and nitric oxide cannot be considered independent predictors of stroke outcome or severity (Steliga *et al.*, 2020; Niak *et al.*, 2023).

GFAP is produced in astrocytes and functions to signal cellular integrity and reactive gliosis. Its production increases in ischemic and hemorrhagic stroke, as well as in traumatic brain injury. GFAP distinguishes between ischemic and hemorrhagic stroke. GFAP is not exclusive to a particular type of stroke and is also activated during traumatic brain injury. In hemorrhagic stroke, the increase in expression is more pronounced than in ischemic infarction. GFAP can aid in differentiating between hemorrhagic and ischemic stroke from 2 to 6 hours after stroke onset. For hemorrhagic stroke, the highest serum levels usually occur between 2 and 6 hours after onset, while in ischemic stroke, serum concentration begins to rise after 24 hours and peaks between the second and third day. In hemorrhagic stroke, there is a connection between lesion size and GFAP serum concentration, but not in ischemic stroke, except after 2 hours from onset. This glycolytic enzyme exhibits expression changes in the acute phase of ischemic stroke. There is a reported correlation between serum NSE levels and the volume of ischemic infarction, making it an indicator of hemorrhagic transformation from an ischemic infarction (Steliga *et al.*, 2020).

In summary, the difficulties in finding suitable biomarkers for ischemic stroke diagnosis arise from the diversity of this clinical condition. Despite the continuous development of new diagnostic methods, identifying cerebral ischemic infarction, particularly in its early stage,

remains highly challenging. Although there are various markers under study, the diagnostic efficacy is still insufficient, especially for multiple types of stroke. This justifies an approach focused on selecting a panel of potential markers with acceptable sensitivity and specificity, linked to the acute or subsequent phases of stroke (Steliga *et al.*, 2020).

The Neurovascular Unit (NVU) is a conglomerate of different elements: neurons, astrocytes, microglia, oligodendrocytes, vascular endothelial cells, perivascular cells, vascular smooth muscle cells, basement membrane, and extracellular matrix. The NVU plays a significant role in the onset and progression of IS. Extracellular Vesicles (EVs) originating from the NVU can act as biomarkers for IS. Compared to bioactive substances in the blood, bioactive substances transported by NVU-derived EVs are more likely to be used as diagnostic and prognostic markers for IS (Gao *et al.*, 2024; Steliga *et al.*, 2020).

Extracellular vesicles are small vesicles surrounded by a lipid bilayer released by various cells through endocytosis. These small vesicles contain different types of molecules, including proteins, lipids, and nucleic acids. They are categorized based on their size as exosomes, microvesicles, or apoptotic vesicles. EVs play a vital role in facilitating material exchange and information transfer between cells, transporting a wide variety of bioactive substances. Based on this, NVU-derived EVs indicate the physiological and pathological condition of the brain cells that produce them. EVs demonstrate the molecular and cellular changes occurring in the brain, which can be detected in minimally invasive procedures, such as blood or CSF samples, facilitating the diagnosis, prognosis, and therapeutic response of diseases such as Alzheimer›s disease (AD), Parkinson›s disease (PD), and multiple sclerosis, besides being biomarkers for ischemic stroke. EVs can also be used to distinguish different locations of ischemic stroke, as the contents of EVs released from different brain regions vary (Gao *et al.*, 2024).

MicroRNAs are small molecules that regulate gene expression by binding to messenger RNAs and inhibiting their translation into proteins. They are used as biomarkers for ischemic stroke and modify the expression of genes involved in neuronal survival, inflammation, and vascular function (Gao *et al.*, 2024). Non-coding RNAs (ncRNAs) have important functions in controlling gene expression and physiological cellular processes. These ncRNAs are abundantly present in mammalian brains, and their alterations appear to have a significant impact on cerebral ischemia and recovery after a stroke. miRNAs are remarkably stable in various biological samples, such as plasma, serum, urine, and cerebrospinal fluid, and can be used as diagnostic, prognostic, or therapeutic biomarkers for various diseases. A significant group of these miRNAs, known as «HypoxamiRs,» is especially upregulated in hypoxic conditions. Among them, miRNA-210 (miR-210) is one of the most prominent, being activated by hypoxia-inducible factor 1 (HIF-1) (Rahmati; Ferns and Mobarra, 2021).

Levels of miR-15a, miR-100, miR-339, and miR-424 in circulating EVs are lower in patients with cortico-subcortical ischemic stroke than in patients with subcortical stroke.

Additionally, EVs can be used as markers to distinguish different stages of cerebral ischemia. Plasma exosomal levels of miR-21-5p in the subacute and recovery phases of stroke were significantly higher than those in other phases. The brain-specific miRNAs miR-9 and miR-124 can be detected in serum EVs. The increase in circulating exosomal levels of miR-122-5p, miR-300-3p, and miR-450b-5p is related to transient ischemic attack (TIA). Both miR-9 and miR-124 are positively associated with National Institutes of Health Stroke Scale (NIHSS) scores, serum IL-6 levels, and infarct volume (Gao *et al.*, 2024).

Patients with IS exhibit higher serum levels of HIF-1α and lower levels of miR-210 than the upper limit of normal. miR-210 was considered a weak diagnostic biomarker upon admission, while HIF-1α was deemed an acceptable diagnostic marker for IS. HIF-1, a crucial component of the hypoxia response, belongs to hypoxia-inducible factors. Under hypoxic conditions, the alpha subunit of HIF-1 (HIF-1α) is stabilized and upregulated. Serum levels of miR-210 significantly changed between admission and 3 months post-IS, whereas serum levels of HIF-1α did not vary significantly during this time interval (Rahmati; Ferns and Mobarra, 2021).

Circulating microRNAs and disease-related blood proteins assist in distinguishing between affected and unaffected patients and predicting associated outcomes (Rahmati; Ferns and Mobarra, 2021). The detection of miR-9 and miR-124 in serum extracellular vesicles is a promising diagnostic approach for ischemic stroke, allowing early diagnosis and assessment of the extent of brain injury (Gao *et al.*, 2024). miR-210 is not viable as a diagnostic marker due to its limited performance, whereas serum HIF-1α may be a useful marker, presenting acceptable sensitivity and specificity (Rahmati; Ferns and Mobarra, 2021). The use of NVU-derived extracellular vesicles represents an emerging field that tends to optimize diagnostic efficiency in the context of ischemic cerebrovascular accidents (Gao *et al.*, 2024).

The candidate gene approach is commonly used to find the genetic reasons for stroke, especially in cases of recurrent events or younger-than-usual age of onset. In this method, genetic variations in a gene known to cause a specific condition are identified. If the condition›s characteristics are not well defined or there are no typical features, the wrong candidate gene may be selected. A limitation of this method is the inability to discover new genetic variations (Ekkert *et al.*, 2021).

Genome-Wide Association Studies (GWAS) present an innovative genetic approach that demonstrates significant efficacy. By genotyping more than a million polymorphisms across the genome simultaneously, GWAS adopts a different method compared to the candidate gene method. GWAS is not limited to a single gene but explores the entire genome, allowing the discovery of new connections between chromosomal loci and diseases. The current difficulty in identifying heritability in specific disease subtypes using GWAS, such as in ischemic stroke, may be attributed to rare and low-frequency variants (Ekkert *et al.*, 2021).

NGS technologies can gather information about entire genomes—whole genome sequencing (WGS)—or protein-coding sequences—whole exome sequencing (WES). The primary goal of NGS is to detect uncommon genetic variations that may not be revealed by GWAS. Its relatively low cost and rapid implementation make it a promising tool not only for research but also for the routine diagnosis of hereditary conditions associated with stroke (Ekkert *et al.*, 2021).

Using weighted gene coexpression network analysis (WGCNA) to validate stroke-associated genetic modules, searching for genes that change over time in stroke progression, and employing different machine learning algorithms (LASSO, SVM-RFE, and Boruta) to discover specific genes involved in stroke, it was found that in the early stages of a stroke, the damaged part of the brain is populated by activated microglia. Highly activated microglia exhibit distinct markers such as Spp1, Lpl, Lgals3, and Cst7. In stroke-related microglia, there is an increase in the expression of Spp1, Lgals3, and Cst7, and diagnostic intervention based on identifying genes attributed to stroke development proved more effective due to the nomogram constructed using machine learning (Song *et al.*, 2023). These innovative techniques provide a new perspective on stroke diagnosis and treatment, enhancing the precision and efficacy of currently used methods.

TREATMENT

Ischemic stroke continues to pose a significant public health challenge due to the scarcity of effective medications and treatment methods. Stroke is the fifth most prevalent cause of mortality worldwide, with 80% of strokes being ischemic events, and an incidence rate of 7.63 million in 2019 (Kamal *et al.*, 2023). Before the 1990s, treatment options for ischemic stroke were limited, primarily focusing on symptomatic management, secondary prevention, and rehabilitation (Herpich; Rincon, 2020). Since then, the field has been transformed by two crucial innovations. The first was the FDA approval of intravenous tissue plasminogen activator (IV-tPA) in 1995, following a seminal study by the National Institute of Neurological Disorders and Stroke (NINDS), marking a significant milestone in the acute treatment of stroke.

For approximately two decades, IV-tPA served as the cornerstone of treatment until advanced clinical trials in the 2010s demonstrated robust results for endovascular therapy (EVT). EVT, which includes mechanical thrombectomy, emerged as an effective intervention to remove larger thrombi, timely restoring cerebral blood flow (Herpich; Rincon, 2020).

Pre-hospital interventions, such as early activation of specialized teams and the use of mobile stroke units equipped with advanced diagnostic technology, have significantly reduced time to treatment, thereby improving clinical outcomes. Moreover, updated guidelines from the American Stroke Association (ASA) and the European Stroke Organization have guided clinical management, ensuring that patients benefit from treatments like alteplase within the therapeutic window of 4.5 hours after symptom onset (Zubair; Sheth, 2021).

Given that ischemic stroke is a devastating condition requiring urgent therapeutic intervention to minimize brain damage and improve clinical outcomes, in addition to thrombolytic and endovascular therapies, there are also studies that include:

- Neuroprotective Agents: Compounds that protect brain cells against ischemia and inflammation-induced damage, such as antioxidants, anti-inflammatory agents, ion channel blockers, among others. However, the efficacy of these agents is limited by their ability to cross the blood-brain barrier (Xu *et al.*, 2023).
- Stem Cell Therapy: Emerging as a promising regenerative strategy, including bone marrow mononuclear cells, adipose tissue-derived stem cells, neural stem cells, and others. These cells have the potential to functionally improve post-stroke recovery, but regulatory challenges and costs remain important considerations (Kawabori *et al.*, 2020).
- Biomarkers: Molecular markers such as GFAP, IL-1β, MMP-9, and miRNAs are used for diagnosis, prognosis, and treatment guidance. They reflect the extent of brain damage, inflammatory response, and blood-brain barrier integrity, providing valuable insights for personalizing therapy and monitoring disease progression (Gao *et al.*, 2024).
- Acetylsalicylic Acid (ASA): Known as aspirin, ASA is used in the secondary prevention of ischemic stroke. It works by inhibiting the production of thromboxane, a pro-coagulant agent, thus reducing the risk of new clot formation and helping to prevent future events (Szczuko *et al.*, 2021).

These therapeutic approaches represent significant advances in managing ischemic stroke, aiming not only to restore cerebral blood flow but also to protect neuronal tissue and improve long-term outcomes for patients affected by this serious and potentially debilitating condition.

Currently, systemic thrombolytic therapy remains the most common therapeutic option in managing ischemic stroke. Based on the goal of recanalizing and reperfusing ischemic areas, this therapeutic method can be adopted up to 4.5 hours after the onset of the ischemic event (Zhao; Zhang; Chen and Wei, 2022). The drug used in systemic thrombolytic therapy is intravenous alteplase at a dose of 0.9 mg/kg, with a maximum dose of 90 mg. Ten percent of the total dose is administered as a bolus, while the remaining 90% is administered over the next hour. Although this is the most used therapeutic method, several patient groups have contraindications to its use. These groups include people with a history of hemorrhagic stroke at any time in life or severe traumatic brain injury or ischemic stroke in the last 3 months, patients with coagulopathies, hypoglycemia, hyperglycemia, severe hypertension (SBP > 185 mmHg or DBP > 110 mmHg), or active intracranial hemorrhage (Zubair; Sheth, 2021). Additionally, the isolated use of alteplase has poor efficacy on occlusions of proximal arteries, such as the internal carotid artery or the proximal portion of the middle cerebral artery (Zhao; Zhang; Chen and Wei, 2022).

The treatment of ischemic stroke faces several challenges that limit the effectiveness of current therapeutic approaches. Endovascular and thrombolytic therapy, although fundamental, faces significant limitations due to the restricted time window and the complexity of managing the blood-brain barrier. Further advances in imaging techniques, such as enhanced perfusion scanning and new high-resolution MRI modalities, have the potential to significantly improve early diagnosis and personalized treatment of stroke. Recent studies have demonstrated that portable low-field MRI can be viable for real-time monitoring in intensive care units, promoting rapid and precise interventions (Zubair; Sheth, 2021).

Additionally, a fundamental challenge lies in the limited understanding of the mechanisms by which circRNAs contribute to ischemic stroke. These circular RNAs play crucial roles in post-transcriptional regulation and modulation of key pathophysiological pathways such as apoptosis, autophagy, and inflammation. However, their exact translation of function is not yet fully elucidated, and it is essential to develop innovative delivery mechanisms that can overcome the restrictions imposed by the blood-brain barrier. The inflammatory response triggered by cell death induced by cerebral ischemia presents itself as a promising therapeutic target (Xu *et al.*, 2023).

Despite the innovations of recent decades that have expanded access to acute stroke treatment and improved clinical outcomes, the stroke mortality rate has stabilized and even increased in certain regions. This phenomenon is attributed to the increase in the prevalence of modifiable risk factors, such as diabetes, hypertension, and hyperlipidemia. Therefore, a renewed focus on educational and preventive strategies is crucial to reduce the incidence of severe or fatal stroke in the future (Herpich; Rincon, 2020).

REFERENCES

EKKERT, Aleksandra, *et al*. Ischemic stroke genetics: what is new and how to apply it in clinical practice?. **Genes**, v. 13, n. 1, p. 48, 2021.

FESKE, Steven K. Ischemic stroke. **The American journal of medicine**, v. 134, n. 12, p. 1457-1464, 2021.

GAO, Xiangyu, *et al.* Revolutionizing Ischemic Stroke Diagnosis and Treatment: The Promising Role of Neurovascular Unit-Derived Extracellular Vesicles. **Biomolecules**, v. 14, n. 3, p. 378, 2024.

HERPICH, Franziska; RINCON, Fred. Management of acute ischemic stroke. **Critical care medicine**, v. 48, n. 11, p. 1654-1663, 2020.

JIA, Junqiu, *et al.* The role of microglial phagocytosis in ischemic stroke. **Frontiers in immunology**, v. 12, p. 790201, 2022.

KAMAL, Fatima Zahra, *et al.* The role of potential oxidative biomarkers in the prognosis of acute ischemic stroke and the exploration of antioxidants as possible preventive and treatment options. **International Journal of Molecular Sciences**, v. 24, n. 7, p. 6389, 2023.

KAWABORI, Masahito, *et al*. Clinical trials of stem cell therapy for cerebral ischemic stroke. **International journal of molecular sciences**, v. 21, n. 19, p. 7380, 2020.

LEE, Yee Teng; MOHD ISMAIL, Nor Ismaliza; WEI, Loo Keat. Microbiome and ischemic stroke: A systematic review. **PLoS One**, v. 16, n. 1, p. e0245038, 2021.

NAIK, Anant, *et al*. Cerebrospinal fluid biomarkers for diagnosis and the prognostication of acute ischemic stroke: a systematic review. **International journal of molecular sciences**, v. 24, n. 13, p. 10902, 2023.

PINTO, S.; HOGAN, C.; BERKHEMER, O.; SHAFAAT, M.; MAZUREK, A. Manejo diagnóstico e terapêutico do acidente vascular cerebral isquêmico no departamento de urgência. **Revista de Fisioterapia**, 2023.

RAHMATI, Mina; FERNS, Gordon A.; MOBARRA, Naser. The lower expression of circulating miR-210 and elevated serum levels of HIF-1α in ischemic stroke; Possible markers for diagnosis and disease prediction. **Journal of Clinical Laboratory Analysis,** v. 35, n. 12, p. e24073, 2021.

SONG, Jingwei, *et al*. Integrative Analysis of Machine Learning and Molecule Docking Simulations for Ischemic Stroke Diagnosis and Therapy. **Molecules**, v. 28, n. 23, p. 7704, 2023.

STELIGA, Aleksandra, *et al.* Neurovascular unit as a source of ischemic stroke biomarkers—limitations of experimental studies and perspectives for clinical application. **Translational stroke research**, v. 11, p. 553-579, 2020.

SZCZUKO, Małgorzata, *et al*. The role of thromboxane in the course and treatment of ischemic stroke. **International Journal of Molecular Sciences**, v. 22, n. 21, p. 11644, 2021.

WANG, Xiaoyu, *et al.* An updated review of autophagy in ischemic stroke: From mechanisms to therapies. **Experimental Neurology**, v. 340, p. 113684, 2021.

XU, Guangchen, *et al*. Circular RNAs: Promising Treatment Targets and Biomarkers of Ischemic Stroke. **International Journal of Molecular Sciences**, v. 25, n. 1, p. 178, 2023.

YANG, Jie, *et al*. Application of radiomics in ischemic stroke. **Journal of International Medical Research**, v. 52, n. 4, p. 03000605241238141, 2024.

ZHAO, Yunfei, *et al*. Neuronal injuries in cerebral infarction and ischemic stroke: From mechanisms to treatment. **International journal of molecular medicine**, v. 49, n. 2, p. 1-9, 2022.

ZUBAIR, Adeel S.; SHETH, Kevin N. Emergency care of patients with acute ischemic stroke. **Neurologic Clinics**, v. 39, n. 2, p. 391-404, 2021.

Chapter 3

ATRIAL FIBRILLATION

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CHAPTER 3

ATRIAL FIBRILLATION

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Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and is associated with a high risk of morbidity and mortality. This condition is related to severe cardiovascular events, such as stroke, heart failure, peripheral embolism, and other causes of death. The pathophysiology of AF is complex and variable among patients, involving mechanisms such as reentry, electrical

and structural modification of atrial tissue, risk factors, genetic predisposition, poor dietary habits, sedentary lifestyle, alcoholism, and the multiple wavelet hypothesis as a perpetuation instrument of AF. Understanding this pathology has evolved substantially in recent decades (Kunal; Wong, 2019; Lau, Linz, and Sanders, 2019).

AF has a high prevalence and elevated morbidity and mortality, affecting approximately 33.5 million people globally. Current therapeutic techniques are effective but have high costs for the healthcare system. Therefore, it is essential to determine modifiable risk factors and implement appropriate preventive measures to improve public health and reduce healthcare system costs (Sagris *et al.*, 2022). The incidence of AF is significant, affecting about 33 million people, and is associated with increased morbidity and mortality, especially in emergency contexts. Risk factors include advanced age, preexisting cardiovascular and chronic diseases, and poor lifestyle habits such as alcoholism. This high incidence requires changes in the structuring of emergency services and the creation of public health policies focused on prevention and rapid patient care (Andersen, Andreasen, and Olesen, 2021).

The diagnosis of AF must be rapid and accurate in medical emergencies. The diagnostic approach includes clinical evaluation of risk factors, genetics, and comorbidities, in addition to complementary tests, with the electrocardiogram being the gold standard. Technological innovations, such as artificial intelligence, have promoted significant advances in the diagnosis of AF, facilitating its therapeutic management (Agewall, 2022; Hendriks *et al.*, 2021). Its treatment is based on heart rate control, reducing its load and duration, preventing thromboembolic events, and restoring sinus rhythm. The therapeutic approach is individualized, considering comorbidities, age, risk factors, and patient genetics (Hendriks et al., 2021).

Urbanization and lifestyle changes, such as inadequate diets and increased sedentary behavior, also play a significant role in the rising incidence of AF. Recent studies have shown that managing lifestyle and risk factors can reverse the progression of AF and maintain sinus rhythm. An integrated care approach has also been effective in reducing cardiovascular hospitalizations and all-cause mortality. Thus, managing risk factors such as obesity, hypertension, and obstructive sleep apnea shows significant impacts on the prevalence and incidence of the pathology. Overweight individuals have a higher risk of developing AF, and changes in weight over time can influence this risk. Comprehensive risk factor management programs have demonstrated that weight loss and improved cardiorespiratory fitness are associated with higher success rates in AF control and treatment (Hendriks *et al.*, 2021; Shamloo *et al.*, 2019).

Recent studies have focused on identifying the cellular and molecular mechanisms leading to atrial remodeling, an important underlying condition in atrial fibrillation (AF) (Lau, Linz, and Sanders, 2019). A significant example of clinical research in this field is the CABANA study (Catheter Ablation vs Antiarrhythmic Drug Therapy in Atrial Fibrillation), which compared the effectiveness of pulmonary vein isolation via catheter ablation with drug

therapy for rate and rhythm control. Although the study demonstrated a significant reduction in AF recurrence in the ablation group, it did not show an improvement in composite clinical outcomes such as mortality, stroke, bleeding, and cardiac arrest compared to the group treated with medications (Wijesurendra and Casadei, 2019).

EPIDEMIOLOGY

Atrial fibrillation (AF) is an arrhythmia whose prevalence increases with age, from less than 0.5% in individuals in their 40s to 10% in those over 80 years old (Huh; Jo, 2023). In 2016, an estimated 463 million individuals worldwide had AF (Kornej *et al.*, 2020). Recent data estimate that one in three people will develop the condition over their lifetime (Alonso, Almuwaqqat, and Chamberlain, 2021). In the United States, between 3 and 6 million people currently suffer from AF, with projections indicating that this number could reach between 6 and 16 million by 2050. In Europe, the prevalence of AF in 2010 was 9 million among individuals over 55, with a projected increase to 14 million by 2060. Over the past 50 years, according to the Framingham Heart Study, the prevalence of atrial fibrillation has tripled, with a lifetime risk estimated at about 1 in 3 for white individuals and 1 in 5 for black individuals. Additionally, the lifetime risk of AF has been estimated at about 1 in 4 white men and women over 40 years old by 2047 (Kornej *et al.*, 2020).

Several factors contribute to these changes. The aging population is one of the main factors, as the prevalence of AF increases substantially with age. Awareness and improved detection of AF have also improved in the last decade, which is crucial given that about one-third of people with AF are asymptomatic (Kornej *et al.*, 2020). In addition to age, the management of risk factors plays a crucial role. Omega-3 fatty acid supplementation, initially considered beneficial for preventing cardiovascular diseases, has shown conflicting results in human studies. Higher doses of omega-3 may increase the risk of AF, especially in individuals with high cardiovascular risk or established cardiovascular diseases (Huh; Jo, 2023). Individuals with multiple risk factors such as obesity, hypertension, diabetes, smoking, and excessive alcohol consumption have an even higher risk of developing AF. Epidemiological studies have demonstrated a strong and independent relationship between obesity and AF, with a 4% to 5% increase in the risk of incidence for each additional unit in body mass index (BMI). Hypertension is also one of the main risk factors, associated with left ventricular hypertrophy and diastolic dysfunction, pathophysiological characteristics of chronic hypertension related to the occurrence of AF. Excessive alcohol consumption and smoking also significantly increase the risk of AF (Shamloo *et al.*, 2019).

Ethnic disparities in detection and treatment, as well as the lack of primary prevention, are significant challenges for the proper management of AF. Studies have revealed that individuals of African or Hispanic descent have lower rates of AF, despite a similar or more severe comorbidity profile compared to individuals of European descent, where for every

10% increase in European genetic ancestry, there is a 13% higher risk of incident AF (Kornej *et al.*, 2020). These discrepancies can be attributed to genetic, socioeconomic, and environmental differences, as well as predisposing factors such as obesity, alcohol, and tobacco consumption that influence both the manifestation and progression of the disease (Andersen, Andreasen, and Olesen, 2021).

Additionally, diagnosing AF often represents a challenge due to the asymptomatic nature of many cases. The use of cardiac monitoring devices has been crucial for detecting AF in patients with cryptogenic stroke, as demonstrated by studies. This method revealed a significant incidence of AF after cerebrovascular events, especially in racially and ethnically diverse populations (Agewall, 2022).

Genetic aspects also influence the predisposition to AF. Genetic variants that encode structural and electrical cardiac proteins have been implicated (Healey, Roberts, and Field, 2021). Studies indicate that people of European descent have a higher risk of AF compared to individuals of African or Asian descent, suggesting that genetic factors may play an important role (Kornej *et al.*, 2020).

Mortality associated with AF has shown decreasing trends in recent decades, attributed to advances in diagnosis, prevention of thromboembolic complications, and better patient management. Oral anticoagulation, for example, has proven effective in reducing strokes and mortality among patients with AF (Alonso, Almuwaqqat, and Chamberlain, 2021).

According to studies, individuals diagnosed with AF have higher cardiovascular disease mortality compared to those without the condition. Women and men with AF showed a 90% and 50% increase in mortality rates, respectively, compared to non-carriers. Recent research indicates a gradual reduction in mortality rates thanks to advances in diagnosis, prevention of thromboembolic complications, and better patient management (Alonso, Almuwaqqat, and Chamberlain, 2021).

Understanding the risk factors associated with AF is crucial for the early identification and effective management of this arrhythmia. Age is one of the most important risk factors, with prevalence increasing substantially in individuals over 40 years old and reaching up to 10% in people over 80 years old (Huh; Jo, 2023). In addition to age, several health conditions play a crucial role, such as arterial hypertension, obesity, heart failure, sleep apnea, diabetes mellitus, coronary artery disease, and chronic kidney disease (Healey, Roberts, and Field, 2021). Smoking is also associated with an increased risk of AF (Shamloo *et al.*, 2019).

DIAGNOSIS

The diagnosis of atrial fibrillation (AF) requires a detailed medical history, physical examination, electrocardiographic evaluation, and complementary tests. The medical history should include an assessment of the patient›s symptoms and a search for factors in the

clinical history related to AF, such as hypertension, hyperthyroidism, structural heart disease (valvular diseases and ischemic disease), and alcohol use, which may be associated with the holiday heart syndrome (Joglar *et al.*, 2024).

AF is the most common sustained cardiac arrhythmia and is associated with adverse outcomes that can be partially prevented by oral anticoagulation. AF meets the World Health Organization (WHO) principles for screening, with the electrocardiogram (ECG) being an important tool for screening undiagnosed AF due to its low cost, safety, and wide acceptance. However, the ECG has a low diagnostic yield (<2%) compared to continuous monitoring through implantable cardiac monitors (ICM) or pacemakers (Extramiana; Steg, 2022).

The 12-lead electrocardiogram (ECG) is the gold standard for the diagnosis of AF. Electrocardiographic findings include irregular RR intervals, absence of P waves, and the presence of f waves (small oscillations in the baseline corresponding to disorganized electrical activity). Patients with a normal ECG at the time of evaluation but with occasional symptoms may undergo ambulatory monitoring with a 24-hour Holter to investigate paroxysmal AF, as well as implantable monitors for long-term monitoring. Electrocardiographic evaluation is also essential to identify coexisting rhythm disturbances, such as atrial arrhythmias and Wolff-Parkinson-White (WPW) syndrome (Joglar *et al.*, 2024). In hospitalized patients, continuous monitoring is crucial for the early detection of acute AF, especially when precipitated by conditions such as sepsis, respiratory failure, or postoperative cardiac surgery. The use of 12-lead ECG remains essential, but telemetry offers the advantage of allowing continuous observation of the heart rhythm (Chyou *et al.*, 2023).

The echocardiogram is essential in the investigation of patients with AF, although it is not used to diagnose the condition itself. Transthoracic echocardiography evaluates valvular function, the size and function of cardiac chambers, with a special focus on the left atrium. The left ventricular ejection fraction (LVEF) impacts decisions on the use of antiarrhythmic medications or other forms of rhythm control, such as ablation. Transesophageal echocardiography is important for investigating interatrial thrombi, especially in patients with a history of AF for more than 48 hours (Joglar *et al.*, 2024).

Techniques for panoramic mapping of cardiac electrical activity have identified two main arrhythmic mechanisms: focal ectopic activations and rotations (rotors). Focal ectopic activities indicate specific areas of the heart where abnormal electrical impulses are generated, which can trigger or perpetuate AF. Rotations are rotational reentrant circuits that maintain the arrhythmia. Studies indicate that rotors detected by phase mapping have low specificity for identifying rotating wave fronts compared to activation time mapping in high-density epicardial electrograms of AF. However, most of these rotors were located near a conduction block line (Lau, Linz, and Sanders, 2019).

Laboratory investigation is indispensable in the workup of patients with AF. Thyroid hormone levels should be measured, as thyrotoxicosis is associated with AF. Laboratory tests

can detect other medical conditions that influence therapeutic decisions, such as chronic kidney disease (CKD) and liver disease (Joglar *et al.*, 2024). The use of mobile and portable devices, such as smartwatches and smartphones with ECG applications, has revolutionized the detection of AF. The Apple Heart Study demonstrated the ability of smartwatches to identify AF episodes with high accuracy in large populations (Seshadri, 2020). Recently, a wearable ECG device in the form of a necklace (Necklace-ECG) showed high sensitivity and specificity in detecting AF, making it a promising solution for screening and diagnosis (Santala *et al.*, 2023). A study evaluated the electrogram morphology recurrence (EMR) mapping technique in 42 patients, showing high recurrence in locations near AF drivers. This innovation could improve diagnostic accuracy and understanding of AF mechanisms, although more studies are needed to confirm its clinical potential (Buch; Du, 2023).

The differential diagnosis of AF includes other supraventricular tachycardias, such as atrial flutter, which can be distinguished on the ECG by the presence of sawtooth F waves and a regular rhythm. Paroxysmal supraventricular tachycardias (PSVT) present with sudden onset and termination and a regular rhythm, while ventricular-origin tachycardias show widened QRS complexes and a regular rhythm, unlike the characteristic irregularity of AF (Joglar *et al.*, 2024).

TREATMENT

Current treatments for AF include rate controllers (beta-blockers, calcium channel blockers, cardiac glycosides), rhythm controllers (antiarrhythmics, electrical cardioversion, catheter ablation), and prevention of thromboembolic events (oral anticoagulation, including warfarin and new oral anticoagulants - NOACs) (Joglar *et al.*, 2024). The use of oral anticoagulants is crucial for patients with AF, reducing the risk of stroke and mortality. Studies show that non-adherence to treatment can significantly increase the risk of adverse events. Healthcare professionals should emphasize the importance of adherence to treatment to improve outcomes and reduce morbidity and mortality (Vitolo *et al.*., 2021).

Modifying risk factors such as obesity and obstructive sleep apnea can reduce the incidence and recurrence of AF. A reduction of at least 5% in body weight, combined with moderate exercise and a balanced diet, has proven effective in controlling AF symptoms. Additionally, the adequate treatment of obstructive sleep apnea with continuous positive airway pressure (CPAP) therapy can reduce the recurrence of AF in patients undergoing electrical cardioversion (Wingerter *et al.*, 2020).

Since the introduction of catheter ablation techniques in 1998, the number of treated patients has increased significantly. Detailed knowledge of cardiac anatomy, including the conduction system (sinoatrial node, atrioventricular node, and His-Purkinje system), is crucial for the success of these interventions. Cryoablation is an effective option for patients with AF refractory to medical treatment, demonstrating superiority over antiarrhythmics for

the initial control of paroxysmal AF (Liu *et al.*, 2023). The success of ablation depends on detailed anatomical knowledge of the cardiac conduction pathways. The sinoatrial (SA) node and the atrioventricular (AV) node play crucial roles in the heart›s electrical conduction, and their integrity must be preserved during surgical procedures. Intraoperative electrophysiological mapping helps identify and protect these nodes, minimizing risks (Cox *et al.*, 2020).

Recent studies investigate the use of ethanol infusion in the vein of Marshall to achieve local parasympathetic denervation and perimitral block. One study reported a positive primary outcome in 51.6% of patients and success in perimitral block in 80.6% (Valderrábano, 2021). This technique, associated with epicardial ablation, may improve the control of persistent AF, but still requires additional confirmation (Valderrábano, 2021).

Gene therapy emerges as a promising approach for the treatment of AF, aiming to replace or remove disease-causing genes in the myocardium. Viral vectors, such as the adeno-associated virus (AAV), are suitable for cardiac gene therapy due to their low immunogenicity and long-lasting expression. Gene therapy can target areas such as ion channels, Ca2+ handling proteins, autonomic nerve remodeling, structural remodeling, inflammatory/oxidative injuries, and apoptosis (Yoo *et al.*, 2021).

The treatment of atrial fibrillation involves a combination of pharmacological, interventional, and lifestyle modification approaches. A detailed understanding of cardiac anatomy and associated risk factors is essential for therapeutic success and complication reduction (Yoo *et al.*, 2021).

REFERENCES

AGEWALL, Stefan. More knowledge about atrial fibrillation, still we need to learn. **European Heart Journal-Cardiovascular Pharmacotherapy**, v. 7, n. 5, p. 361-362, 2021.

ALONSO, Alvaro; ALMUWAQQAT, Zakaria; CHAMBERLAIN, Alanna. Mortality in atrial fibrillation. Is it changing?. **Trends in cardiovascular medicine**, v.31, n.8, p.469-473, 2021.

ANDERSEN, Julie H.; ANDREASEN, Laura; OLESEN, Morten S. Atrial fibrillation—a complex polygenetic disease. **European Journal of Human Genetics**, v.29, n.7, p.1051-1060, 2021.

BUCH, Eric; DO, Duc H. Mapping Persistent Atrial Fibrillation: Searching for Signal in the Noise. **Clinical Electrophysiology**, ,v.9, n. 4, p. 541-542, 2023.

CHYOU, Janice Y., *et al.* Atrial fibrillation occurring during acute hospitalization: A scientific statement from the American Heart Association. **Circulation**, v.147, n.15, p. e676-e698, 2023.

COX, James L., *et al.* Cardiac anatomy pertinent to the catheter and surgical treatment of atrial fibrillation. **Journal of cardiovascular electrophysiology**, v. 31, n. 8, p. 2118-2127, 2020.

EXTRAMIANA, Fabrice; STEG, Philippe Gabriel. Atrial fibrillation screening: the tools are ready, but should we do it?. **Circulation**, v.145, n.13, p. 955-958, 2022.

HEALEY, Jeff S.; ROBERTS, Jason D.; FIELD, Thalia S. Who is at risk of atrial fibrillation?. **Heart Rhythm**, v.18, n.6, p.853-854, 2021.

HENDRIKS, Jeroen M., *et al*. Risk factor management and atrial fibrillation. **EP Europace**, v.23, p. ii52-ii60, 2021.

KORNEJ, Jelena, *et al*. Epidemiology of atrial fibrillation in the 21st century: novel methods and new insights. **Circulation research**, v.127, n.1, p. 4-20, 2020.

LAU, Dennis H.; LINZ, Dominik; SANDERS, Prashanthan. New findings in atrial fibrillation mechanisms. **Cardiac electrophysiology clinics**, v.11, n.4, p.563-571, 2019.

LIU, Zirui, *et al*. Short-term and long-term effects of cryoballoon ablation versus antiarrhythmic drug therapy as first-line treatment for paroxysmal atrial fibrillation: A systematic review and meta-analysis. **Clinical Cardiology**, v.46, n.10, p.1146-1153, 2023.

SANTALA, Onni E., *et al*. Necklace-embedded electrocardiogram for the detection and diagnosis of atrial fibrillation. **Clinical Cardiology**, v. 44, n.5, p. 620-626, 2021.

SESHADRI, Dhruv R., *et al*. Accuracy of Apple Watch for detection of atrial fibrillation. **Circulation**, v.141, n. 8, p. 702-703, 2020.

SHAMLOO, Alireza Sepehri, *et al.* Atrial fibrillation: A review of modifiable risk factors and preventive strategies. **Romanian Journal of Internal Medicine**, v.57, n.2, p.99-109, 2019.

VALDERRÁBANO, Miguel. Vein of Marshall ethanol infusion in the treatment of atrial fibrillation: from concept to clinical practice. **Heart Rhythm**, v.18, n.7, p. 1074-1082, 2021.

VITOLO, Marco, *et al*. The importance of adherence and persistence with oral anticoagulation treatment in patients with atrial fibrillation. **European Heart Journal-Cardiovascular Pharmacotherapy**, v. 7, p. f81-f83, 2021.

WIJESURENDRA, Rohan S.; CASADEI, Barbara. Mechanisms of atrial fibrillation. **Heart**, v.105, n. 24, p.1860-1867, 2019.

WINGERTER, Rebecca, *et al.* Impact of lifestyle modification on atrial fibrillation. **The American Journal of Cardiology**, v.125, n.2, p. 289-297,2020.

YOO, Shin, *et al*. Recent advances in gene therapy for atrial fibrillation. **Journal of cardiovascular electrophysiology**, v.32, n.10, p. 2854-2864, 2021.

Chapter 4

ACUTE RESPIRATORY FAILURE

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CHAPTER 4

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Acute Respiratory Failure (ARF) is a critical medical condition characterized by abnormal pulmonary mechanics, impaired gas exchange, or disturbances in pulmonary circulation. In this condition, the concentration of oxygen in the blood can be insufficient for the body›s metabolic demands, caused by various diseases. Lack of adequate treatment can lead to irreversible consequences and fatal complications, requiring immediate medical intervention and highlighting its high clinical relevance (Yang; Esper, 2024).

ARF is among the most common causes of critical illness, with a hospital mortality rate of approximately 30% (Yang; Esper, 2024). In the United States, more than one million patients admitted annually to intensive care units (ICUs) require mechanical ventilation for acute respiratory failure. Advances in intensive care have reduced mortality rates, resulting in an increasing number of survivors. However, 65% of these survivors experience significant functional disability, negatively affecting quality of life and potentially persisting for years after hospitalization for ARF. Despite evidence that functional disability is a common problem for ARF survivors, early identification and management are still poorly studied and understood. Identifying the various subtypes of ARF patients early in the ICU stay can help personalize interventions and strategically plan the prognosis to improve quality of life after hospitalization (Potter *et al.*, 2023).

ARF is one of the conditions with the highest incidence in ICUs, representing 56% to 69% of admissions, in addition to having a high financial cost for the healthcare system (Yang; Esper, 2024). The main causes of death in patients with ARF are linked to sepsis, pulmonary, and neurological dysfunction, demonstrating that therapies focused on reducing sepsis complications increase the survival of these patients (Ketcham et al., 2020). Rapid diagnosis is essential, given the impact of functional disability and high mortality in emergencies (Potter *et al.*, 2023). However, early identification is challenging due to the rapid progression of the condition, the wide variety of causes, clinical presentation, and patient heterogeneity (Yang; Esper, 2024).

Strategies for managing ARF consist of nonspecific supportive measures and individualized treatment approaches. The use of latent class analysis to identify patterns of functional impairment and mobility allows for a more personalized and effective approach. Additionally, interventions to improve physical function post-ICU have been explored, although they need more evidence-based investigations. Recent studies highlight strategies such as the adoption of lung-protective ventilation with reduced tidal volumes to minimize ventilator-induced lung injuries. Early mobilization of ICU patients, including physical and occupational therapy, has shown benefits in reducing muscle weakness and improving physical function post-ICU (Ketcham *et al.*, 2020).

Another important trend is the use of biomarkers for the identification and monitoring of conditions associated with ARF, such as inflammatory cytokines and lung injury markers. These biomarkers can aid in early diagnosis, prognosis, and the development of targeted therapies. Additional supportive therapies, such as high-flow oxygen therapy, positional therapy, and pulmonary rehabilitation, are being integrated into ARF management to optimize patient recovery (Yang; Esper, 2024).

The use of adjunct therapies, such as prone positioning in patients with Acute Respiratory Distress Syndrome (ARDS), aggressive management of sepsis associated with ARF, and promotion of early mobilization in patients on mechanical ventilation, aims to reduce complications and improve rehabilitation. The multidisciplinary and individualized approach to ARF patients, including specialized intensive care teams, is crucial for improving clinical outcomes (Ketcham *et al.*, 2020).

EPIDEMIOLOGY

According to recent data, the incidence of Acute Respiratory Distress Syndrome (ARDS) varies significantly across different regions of the world. In 2014, the incidence in Brazil was 10.1 per 100,000 inhabitants per year, while in the United States, it was 82 per 100,000 inhabitants per year in 2005. Respiratory failure is one of the leading causes of mortality in ICUs worldwide. In Scandinavia, the mortality rate for ARDS is 41%, and for acute lung injury (ALI) it is 42.2%. In the United States, the mortality rate varied from 5.01 per 100,000 people in 1999 to 2.82 per 100,000 inhabitants in 2013 (Ernest, 2020; Hendrickson, Peltan, and Brown, 2021).

In recent years, there have been changes in the incidence and mortality of respiratory failure, attributed to advances in diagnostic methods, an increase in patients with chronic comorbidities, a decrease in individuals over 70 years old, and the admission of patients with greater severity. There was a 197% increase in incidence, from 429 to 1,275 cases per 100,000 adults per year, and a 57% decrease in mortality, from 28% to 12%. This indicates that mortality has improved despite the increased severity and incidence of the disease, possibly due to improvements in intensive care (Kempker *et al.*, 2020).

In certain studies, during the analysis period, hospital mortality decreased from 34% to 23%. This variation is attributed to changes in patient characteristics over the study period. A decrease in the proportion of patients aged 70 years or older, an increase in the proportion of patients with chronic comorbidities, an increase in the proportion of patients at higher risk of disease severity, and an increase in the proportion discharged to intermediate care units were observed, along with a reduction in hospital length of stay (Kempker *et al.*, 2020).

The risk factors for respiratory failure interact in a complex manner. Chronic alcohol use causes pulmonary immunodepression, epithelial dysfunction, and an inability to contain reactive oxygen species, resulting in high permeability pulmonary edema and hyaline membrane formation. Smoking, on the other hand, increases the expression of the inflammatory cascade, leading to ARDS conditions. Advanced age is related to an increased incidence, however, it has not been found to be associated with increased mortality. Diabetes is associated with a lower incidence of the disease, possibly contributing to the attenuation of the systemic inflammatory response (Hendrickson, Peltan, and Brown, 2021).

DIAGNOSIS

Acute Respiratory Failure (ARF) can be caused by various primary conditions such as bacterial pneumonia, viral infections, drug-induced lung injury, and acute exacerbation of interstitial lung disease. Early diagnosis and immediate intervention are crucial for saving lives (Anan *et al.*, 2022). The management of ARF consists of a cyclical process involving

three stages: verification, treatment, and maintenance. In the verification stage, the level of consciousness, respiratory rate, pulse oximetry, blood gas analysis, and underlying cause are assessed (See, 2022).

Acute hypoxemic respiratory failure is characterized by a sudden decrease in the partial pressure of arterial oxygen (PaO_2) to <60 mmHg, corresponding to an arterial oxygen saturation <90% and reflecting SpO_2 <90%. Additionally, it may be accompanied by an elevation in $PaCO_2$ to >45 mmHg and a decrease in blood pH to <7.35 (i.e., acidemia), leading to acute hypercapnic respiratory failure. This state is potentially fatal, as the concentration of oxygen in the blood may be insufficient for organ demands, resulting in tissue hypoxia (See, 2022).

Initially, ARF can be identified by a decreased level of consciousness or abnormal respiratory rate, caused by either hypoxemia or hypercapnia. Pulse oximetry, a non-invasive method, is used to confirm hypoxemia by detecting pulsatile flow and calculating the ratio of oxygenated to deoxygenated hemoglobin. Arterial blood gas analysis is used to evaluate hypercapnia by checking the acid-base balance. The severity of ARF can be estimated by the ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (See, 2022).

In critically ill patients with ARF, lung ultrasound is a useful tool for rapid diagnosis and therapeutic management. It diagnoses conditions such as pneumothorax, acute respiratory distress syndrome (ARDS), cardiogenic pulmonary edema, pneumonia, and acute pulmonary embolism by evaluating the four intercostal spaces in each hemithorax, looking for the pleural line, A-lines, B-lines, alveolar consolidation, and pleural effusion (Islam *et al.*, 2020).

Cellular analysis through bronchoalveolar lavage (BAL) can be a useful diagnostic method, especially for uncommon causes of ARF, such as pneumocystis pneumonia and invasive pulmonary aspergillosis. BAL is safe even in patients with severe ARF, including those on mechanical ventilation, with a low risk of death, severe cardiovascular complications, and bleeding. However, the patient›s preexisting comorbidities, especially cardiovascular ones, should be considered as they can cause hemodynamic instability during the procedure (Anan *et al.*, 2022).

Lung biopsy can be useful in diagnosing ARF and ARDS, although its feasibility and safety still need to be better established. Recent studies indicate that lung biopsy for ARDS or ARF is safe, with fewer than 5% of severe complications such as bleeding, infections, and persistent air leaks, and no related deaths reported (Sugimoto *et al.*, 2023).

The biomarker MV-miR-223 emerges as a new option for evaluating the prognosis in patients with ARDS. These microRNAs regulate the hematopoiesis of myeloid lineage cells and granulocytic degranulation and are strong markers of inflammatory response in acute lung injury. The ALTA study concluded that elevated levels of MV-miR-223 are associated with severe lung injury and worse prognosis. However, limitations such as differences between control and ARDS plasma samples and the small sample size make the study less conclusive (Almuntashiri *et al.*, 2022).

TREATMENT

Given the prevalence of hypoxemic acute respiratory failure (ARF), which accounts for a high number of intensive care unit (ICU) admissions, effective management is essential to improve patient survival (Grieco *et al.*, 2021). Intubation and the use of non-invasive mechanical ventilation are evident in two-thirds of these cases, with a mortality rate exceeding 50%, emphasizing the importance of oxygenation therapies that aim to avoid intubation (Coudroy *et al.*, 2019). The use of non-invasive oxygenation, such as high-flow nasal oxygen (HFNO), non-invasive ventilation (NIV) with a helmet or facial mask, and continuous positive airway pressure (CPAP), are frequently employed in these patients. These methods have shown benefits compared to standard oxygen therapy, avoiding endotracheal intubation in patients with mild hypoxemia (Grieco *et al.*, 2021).

Non-invasive ventilation can be performed using bilevel positive airway pressure (BPAP) or continuous positive airway pressure (CPAP). It can be offered through different interfaces, such as facial masks and helmets, depending on the patient, the objective, and comorbidities. Below are the main benefits of these modalities:

High-Flow Nasal Cannula (HFNC)

- Settings: FiO_2 0.21 – 1; airflow 40-60 lpm; temperature 31-37ºC.
- Benefits: Matches inspiratory flow; delivers total FiO_2; provides conditioned gas; improves comfort; provides positive pressure up to 4 cmH_2O; washes out dead space in the nasopharynx and reduces inspiratory effort.
- Obstacle: Limited amount of PEEP provided.

Facial Mask:

- Settings: PSV requires a ventilator; FiO_2 0.12 – 1; PEEP 5-8 cmH_2O; PS 7-10 cmH_2O; CPAP, continuous flow >30 l/min.
- Benefits: Provides defined FiO_2; conditioned gas; PEEP allows alveolar recruitment; PS unloads inspiratory muscles; tidal volume monitoring.
- Obstacles: Skin ulcers; air leakage; difficulty with high PEEP; low tolerance; increased transpulmonary pressure and tidal volume.

Helmet:

- Settings: PSV requires a ventilator; FiO_2 0.21 – 1; PEEP 10-12 cmH_2O; PS 10-12 cmH_2O; no need for humidification; rapid pressurization with CPAP; continuous flow >60 l/min.
- Benefits: Provides defined FiO_2; alveolar recruitment with high PEEP; good tolerance; PS reduces inspiratory effort; asynchronous PS can prevent increased transpulmonary pressure.

- Obstacles: Inability to measure tidal volume; upper limb edema with potential venous thrombosis.

Benefits of NIV:

BPAP is widely used in patients with acute hypercapnic respiratory failure, such as those with exacerbation of chronic obstructive pulmonary disease (COPD) or disorders that evolve with acute hypoventilation. Patients with acute hypoxemic non-hypercapnic respiratory failure, such as those with asthma, acute respiratory distress syndrome (ARDS), and pneumonia, also benefit from BPAP. On the other hand, CPAP is primarily designated for patients with acute cardiogenic pulmonary edema (Hyzy; McSparron, 2020).

The use of non-invasive therapies allows patients to benefit from spontaneous breathing, preserving physiology and reducing complications related to invasive mechanical ventilation, such as diaphragmatic atrophy. However, spontaneous breathing can cause damage due to unregulated respiratory effort and lung mechanics, resulting in patient self-inflicted lung injury (P-SILI). Thus, patients with greater severity and a tendency to fail NIV may be less benefited by its use (Grieco *et al*., 2021).

High-Flow Nasal Oxygen Therapy (HFNO):

High-flow nasal oxygen therapy (HFNO) has gained prominence due to its clinical efficacy, providing a high flow mixture of humidified and heated air. HFNO can increase airway pressure proportionally to the end-expiratory volume, leading to efficient alveolar recruitment and reducing inspiratory effort and respiratory rate. Compared to conventional devices, HFNO allows for a higher inspiratory flow, eliminating anatomical dead space and improving functional residual capacity (Vega & Pisani, 2021; Ricard *et al*., 2020).

Rigorous monitoring is essential to avoid delays in endotracheal intubation when there are signs of clinical deterioration, such as muscle fatigue, need for vasoactive drugs, cardiac dysfunction, and organ failure (Ricard et al., 2020). Parameters such as oxygenation through pulse oximetry, arterial blood gas analysis, ROX index, HCOR scale, expired tidal volume, and inspiratory effort are used for monitoring (Grieco *et al*., 2021).

Indicators of Failure in NIV and HFNO:

- SpO_2/FiO_2: Risk of failure when <120 or worsening trend.
- PaO_2/FiO_2: Risk of failure when <150-200 mmHg or worsening trend.
- Respiratory Rate: Risk of failure when >25-30 or not decreasing with support.
- Expired Tidal Volume: Risk of failure when >9-9.5 ml/kg of predicted body weight.
- Transpulmonary Pressure: Risk of failure when >15 cmH_2O or reduction of <10 cmH_2O during NIV.

- ROX Index: Risk of failure when <2.85 at 2 hours, <3.47 at 6 hours, or <3.85 at 12 hours of HFNO initiation.
- HCOR Scale: Risk of failure when >5 one hour after NIV initiation.

An innovative pillar in the treatment of ARF is the study of microbiomes, suggesting that respiratory microbiota patterns are predictive of increased mortality among critically ill patients. Oropharyngeal swab and endotracheal aspirate samples were analyzed with 16s ribosomal RNA gene sequencing, along with inflammatory biomarkers such as receptor for advanced glycation end products and interleukin-10. Future therapies may be guided by patterns of dysbiosis or direct manipulation of the host microbiome (Ali & Sweeney, 2020).

High-Flow Nasal Cannula (HFNC)

HFNC is indicated for acute hypoxemic respiratory failure as an alternative to NIV, during NIV intervals, in postoperative patients at risk of pulmonary complications, and in cases of extubation failure. HFNC has shown similar efficacy to NIV in terms of intubation rate, mortality, and treatment failure, along with better patient tolerance, which reduces the rate of therapeutic failure (Oczkowski et al., 2022; Xu et al., 2023).

Invasive Mechanical Ventilation (IMV)

IMV, in turn, is indicated in cases of severe hypoxemic or hypercapnic respiratory failure that do not respond to NIV. Evidence-based practice (EBP) associated with IMV is linked to lower mortality rates. Interventions such as daily sedation interruptions, mobility exercises, and spontaneous breathing trials help reduce the duration of IMV and improve clinical outcomes (Ervin *et al.*, 2020).

Indications:

- Acute hypercapnic respiratory failure (exacerbation of COPD)
- Acute respiratory failure due to cardiogenic pulmonary edema
- Acute hypoxemic non-hypercapnic respiratory failure
- Asthma exacerbation, among others.

Contraindications:

- Need for emergency intubation
- Acute non-respiratory organ failure with life-threatening risk
- Facial abnormalities
- Significant airway obstruction
- Inability to protect the airways
- Prolonged duration of ventilatory support (Hyzy; McSparron, 2022).

REFERENCES

ALI, Farhana; SWEENEY, Daniel A. In pursuit of microbiome-based therapies for acute respiratory failure. **American Journal of Respiratory and Critical Care Medicine**, v. 202, n. 12, p. 1616-1618, 2020.

ALMUNTASHIRI, Sultan et al. Identification of circulating microvesicle-encapsulated miR-223 as a potential novel biomarker for ARDS. **Physiological reports**, v. 10, n. 21, p. e15494, 2022.

ANAN, Keisuke et al. Safety and harms of bronchoalveolar lavage for acute respiratory failure: A systematic review and meta-analysis. **Respiratory Investigation**, v. 60, n. 1, p. 68-81, 2022.

COUDROY, Rémi et al. High-flow nasal oxygen therapy alone or with non-invasive ventilation in immunocompromised patients admitted to ICU for acute hypoxemic respiratory failure: the randomised multicentre controlled FLORALI-IM protocol. **BMJ open**, v. 9, n. 8, p. e029798, 2019.

ERNEST, Vergel. Respiratory failure: Classification, Epidemiology and Etiology Review. **Journal La Medihealtico,** v. 1, n. 2, p. 15-20, 2020.

ERVIN, Jennifer N. et al. Evidence-based practices for acute respiratory failure and acute respiratory distress syndrome: a systematic review of reviews. **Chest**, v. 158, n. 6, p. 2381-2393, 2020.

GRIECO, Domenico Luca et al. Non-invasive ventilatory support and high-flow nasal oxygen as first-line treatment of acute hypoxemic respiratory failure and ARDS. **Intensive care medicine**, v. 47, p. 851-866, 2021.

HENDRICKSON, Kathryn W.; PELTAN, Ithan D.; BROWN, Samuel M. The epidemiology of acute respiratory distress syndrome before and after coronavirus disease 2019. **Critical care clinics**, v. 37, n. 4, p. 703-716, 2021.

HYZY, Robert C.; MCSPARRON, Jakob I. Noninvasive ventilation in adults with acute respiratory failure: Benefits and contraindications. **UptoDate**. Literature review current through: Jun, 2022.

HYZY, Robert C.; MCSPARRON, Jakob I. Noninvasive ventilation in adults with acute respiratory failure: Practical aspects of initiation. **UpToDate**. Abril de, 2020.

ISLAM, Marjan et al. Lung ultrasound for the diagnosis and management of acute respiratory failure. **Lung**, v. 198, p. 1-11, 2020.

KEMPKER, Jordan A. et al. The epidemiology of respiratory failure in the United States 2002–2017: a serial cross-sectional study. **Critical Care Explorations**, v. 2, n. 6, p. e0128, 2020.

KETCHAM, Scott W. et al. Causes and characteristics of death in patients with acute hypoxemic respiratory failure and acute respiratory distress syndrome: a retrospective cohort study. **Critical Care**, v. 24, p. 1-9, 2020.

OCZKOWSKI, Simon et al. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. **European respiratory journal,** v. 59, n. 4, 2022.

POTTER, Kelly M. et al. Identifying Comorbid Subtypes of Patients With Acute Respiratory Failure. **American journal of critical care**, v. 32, n. 4, p. 294-301, 2023.

RICARD, Jean-Damien et al. Use of nasal high flow oxygen during acute respiratory failure. **Intensive care medicine**, v. 46, p. 2238-2247, 2020.

SEE, Kay Choong. Approach to acute respiratory failure for frontline clinicians. **Singapore Medical Journal**, v. 63, n. 12, p. 740-745, 2022.

SUGIMOTO, Hiroshi et al. Complications of a lung biopsy for severe respiratory failure: A systematic review and meta-analysis. **Respiratory Investigation**, v. 61, n. 1, p. 121-132, 2023.

VEGA, M. L.; PISANI, L. Nasal high flow oxygen in acute respiratory failure. **Pulmonology**, v. 27, n. 3, p. 240-247, 2021.

XU, Cuiping et al. Comparison of High Flow Nasal Therapy with Non-Invasive Ventilation and Conventional Oxygen Therapy for Acute Hypercapnic Respiratory Failure: A Meta-Analysis of Randomized Controlled Trials. **International Journal of Chronic Obstructive Pulmonary Disease**, p. 955-973, 2023.

YANG, Philip; ESPER, Annette M. Acute Respiratory Failure: Problems Solved and Unsolved. **Critical Care Clinics**, 2024.

Chapter 5

THYROTOXIC CRISIS

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Thyroid storm, also known as thyrotoxic crisis, is a severe and potentially fatal complication of thyrotoxicosis. This condition manifests rapidly and is associated with high rates of morbidity and mortality, requiring immediate recognition and treatment. Although rare, thyroid storm can be triggered by factors such as surgery, trauma, infection, or changes in medication. The diagnosis and treatment of

this condition remain challenging as there are no specific laboratory abnormalities to identify it, and the available scoring system is based on clinical criteria (Ross, 2023).

Thyroid hormones affect all body systems and, in excess, can increase metabolic rate, heart rate, ventricular contractility, and gastrointestinal motility, as well as cause excitability of the muscles and central nervous system. Thyrotoxicosis results from an excessive concentration of these hormones, and thyroid storm is its most extreme form. While the exact mechanism of thyroid storm is not fully understood, it is believed to occur due to an increased tissue response to thyroid hormones, greater binding to thyroid receptors, decreased binding protein affinity, or a sudden increase in the availability of free thyroid hormones (Idrose, 2015).

In emergency and critical care settings, thyroid storm is a critical condition requiring immediate attention and intensive treatment, often in an ICU environment. It is essential to provide advanced supportive care to manage potential complications, such as severe cardiovascular events, liver dysfunction, and even mortality. Despite available treatments, mortality rates remain high, underscoring the importance of early diagnosis and rapid intervention (Chiha, Samarasinghe and Kabaker, 2015).

Thyrotoxicosis is relatively common, with the prevalence of hyperthyroidism ranging from 0.05% to 1.3% in the U.S. Thyroid storm, though rare, has a high mortality rate, reaching 80-100% without treatment and 10-50% with treatment. Studies in Japan show an incidence of 0.20 cases per 100,000 people per year among hospitalized patients. Rates of thyrotoxicosis vary geographically, being more common in regions with iodine deficiency. Graves› disease is the primary cause of hyperthyroidism in areas with adequate iodine intake and is 10 times more common in women. Thyroid storm is more frequent in young women but can affect any age group. Risk factors include a history of thyroid disease, female gender, reproductive age, iodine intake, use of medications such as amiodarone, and precipitating conditions like infections and trauma. Understanding these epidemiological aspects is crucial for early diagnosis and proper management of these conditions to reduce associated mortality (Idrose, 2015).

The diagnosis of thyrotoxicosis and thyroid storm involves identifying clinical signs such as weight loss, tremors, heat intolerance, tachycardia, and hypertension, confirmed by laboratory tests, including measurements of high T3 and T4 levels and low TSH levels, elevated CRP (C-reactive protein) levels, and monitoring of liver and kidney function. Biotin can interfere with laboratory results, leading to falsely low TSH and thyroglobulin readings, and falsely high T3 and T4 (Ylli, Klubo-Gwiezdzinska and Wartofsky, 2019).

Clinical criteria, such as the Burch-Wartofsky scoring system, are used to assess severity. Additional tests like ECG and chest X-ray may be performed to evaluate complications, while a detailed medical history is crucial to identify precipitating factors such as amiodarone use or iodine exposure. Rapid and accurate diagnosis is essential to initiate appropriate treatment and reduce associated mortality (Ross, 2023).

Imaging technologies include ultrasound to evaluate the thyroid gland, thyroid scintigraphy to assess radioactive iodine uptake, ECG to monitor and detect arrhythmias, and echocardiography to evaluate cardiac function in patients with heart failure symptoms. Emerging biomarkers are also being studied to improve diagnostic accuracy and monitor treatment response, although they are not yet widely implemented in daily clinical practice (Algell *et al.*, 2015).

The treatment of thyrotoxicosis and thyroid storm involves multiple therapeutic approaches. Antithyroid medications such as methimazole and propylthiouracil reduce hormone production, while beta-blockers control adrenergic symptoms. Iodine can be used to temporarily block hormone production. In severe cases, corticosteroids may be administered. Definitive options include surgery and radioactive iodine for selected cases. Clinical support is essential, with rigorous monitoring and intensive care when necessary. The therapeutic approach is personalized, aiming to stabilize patients and prevent severe complications (Chiha, Samarasinghe and Kabaker, 2015). Updated guidelines for thyroid storm have been developed by the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE), focusing on the efficacy of new therapeutic approaches such as plasmapheresis and combined therapies of antithyroid drugs and glucocorticoids, showing improvements in clinical outcomes (Algell *et al.*, 2015).

Recent treatment techniques with pharmacological therapy include the use of beta-blockers to control adrenergic symptoms, antithyroid drugs to inhibit thyroid hormone synthesis, potassium iodide to inhibit hormone release from the thyroid, and glucocorticoids to reduce the conversion of T4 to T3 and treat relative adrenal insufficiency. In severe cases, intravenous administration of levothyroxine (T4) or triiodothyronine (T3) may be used (Ylli, Klubo-Gwiezdzinska and Wartofsky, 2019).

Adjuvant therapies include plasmapheresis in refractory or severe cases and rectal administration of medications in patients unable to take oral medications. Supportive management involves intensive care, rigorous monitoring to manage severe complications, treatment of precipitating causes, and fluid and electrolyte replacement (Algell *et al.*, 2015).

EPIDEMIOLOGY

Thyroid storm is a rare but severe condition, with an incidence ranging from 0.20 to 0.76 per 100,000 people per year, and 4.8-5.6 per 100,000 hospitalized patients. It is a high-mortality condition that requires immediate recognition and treatment. Understanding its epidemiology, risk factors, and demographics is crucial to improving early diagnosis and effective management, reducing mortality, and enhancing clinical outcomes for affected patients. In the United States, 16% of hospitalized patients with thyrotoxicosis are diagnosed with thyroid storm (Farooqi *et al.*, 2023). The reduction in the incidence of this condition is largely due to early diagnosis and screening for hyperthyroidism (Idrose, 2015).

The mortality rate of untreated thyroid storm is alarming, ranging from 80% to 100%, while with treatment, this rate decreases to between 10% and 50%. Recent studies indicate significant improvement in the United States, with mortality rates reduced to 1.2% to 3.6%, thanks to intensive and high-quality treatments (Idrose, 2015; Farooqi *et al.*, 2023). Patients with high levels of total bilirubin (>3 mg/dL) have significantly higher mortality.

The most common causes of death include multiple organ failure, congestive heart failure, respiratory failure, arrhythmias, disseminated intravascular coagulation, gastrointestinal perforation, cerebral hypoxia, and sepsis (Idrose, 2015). Graves› disease is the main cause of thyroid storm due to excessive and uncontrolled stimulation of thyroid hormones, being more common in young women, who are affected ten times more than men at any age (Chiha, Samarasinghe and Kabaker, 2013).

Precipitating factors include trauma, thyroiditis, excessive manipulation of the thyroid gland, use of medications such as anesthetics, salicylates, pseudoephedrine, and amiodarone, withdrawal of antithyroid treatment, cerebrovascular incidents, and acute ingestion of high doses of thyroid hormone (Idrose, 2015; Chiha, Samarasinghe and Kabaker, 2013). Infections are currently the most common cause of thyroid storm in hospitalized patients. In about 25% to 43% of patients, no clear precipitating factor is identified.

Exogenous causes, such as metastatic thyroid carcinomas, ectopic thyroid tissue, or excessive thyroid hormone ingestion, can also lead to thyrotoxicosis (Idrose, 2015). Thyroid storm is an extreme response of thyrotoxicosis, more common in women and often associated with Graves› disease, with an estimated incidence of 0.2 per 100,000 per year among Japanese patients (Chiha, Samarasinghe and Kabaker, 2013).

Although the overall incidence of thyroid storm has declined due to early screening for hyperthyroidism, thyrotoxicosis continues to have a significant incidence, between 0.05% and 1.3% in the United States, with most cases being subclinical (Idrose, 2015). Early screening allows for faster diagnosis and better prevention, reducing associated mortality.

Thyrotoxicosis without thyroid storm is more common in middle-aged adults, Caucasians, and women. Among hospitalized patients in the United States, thyroid storm is more frequent among Hispanics and African Americans. Graves› disease, discontinuation of medications, and younger age (18-40 years) are significant risk factors (Galindo *et al.*, 2019). Patients with Graves› disease have a higher prevalence of thyroid storm, with a significant incidence of medication discontinuation, reflecting the importance of continuous and proper management of antithyroid treatment. Young and adult patients have a lower risk of mortality, underscoring the need for constant vigilance and early interventions.

DIAGNOSIS

The use of scoring systems based on clinical findings, such as the Burch-Wartofsky Point Scale, is crucial for identifying this condition (Banerjee; Bala and Aggarwal, 2019). Additionally, other important diagnostic systems include the Japanese Thyroid Association criteria and the Akamizu Criteria, which integrate clinical findings with laboratory results and thyroid hormone levels (Elendu *et al.*, 2024).

The role of imaging studies, such as ultrasound and fine-needle aspiration biopsy (FNAB) for incidental nodules, needs to be re-evaluated (Shnadig, 2014). Recent research highlights elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6) as important markers for screening thyroid storm (Elendu et al., 2024). Technological innovations, such as artificial intelligence algorithms, promise to revolutionize early diagnosis and prevention of this emergency by cross-referencing laboratory data, imaging studies, and clinical symptoms (Elendu *et al.*, 2024).

The condition can be excluded if the patient presents with unexplained diseases such as pneumonia, malignant hyperthermia, psychiatric disorders, cerebrovascular disorders, acute myocardial infarction, viral hepatitis, and acute liver failure (Akamizu *et al.*, 2012). However, these disorders can trigger thyrotoxic crises. Triggering factors for thyrotoxic crises include irregular use or discontinuation of antithyroid medications, thyroid surgery, radioactive thyroid therapy, excessive palpation or biopsy, infection, trauma, pregnancy and childbirth, adrenal insufficiency, diabetic ketoacidosis, administration of iodinated contrast media, cerebrovascular disorders, pulmonary thromboembolism, ischemic heart diseases, tooth extraction, severe emotional stress, and strenuous exercise (Akamizu *et al.*, 2012).

The Burch-Wartofsky Point Scale is widely used, based on clinical signs and symptoms, while the Japanese Thyroid Association Criteria rely on clinical findings and laboratory results, and the Akamizu Criteria include clinical characteristics and thyroid hormone levels such as free thyroxine (FT4). Diagnosis is particularly challenging due to the variety of symptoms overlapping with other diseases such as sepsis, drug intoxication, and heart failure. For pediatric patients, the Adapted Burch-Wartofsky Criteria are used, considering the specific vital signs and symptoms for each age group. In elderly patients, diagnosis requires caution, as they may not present common symptoms such as high fever and hyperactivity (Akamizu *et al.*, 2012).

The differential diagnosis of thyrotoxic crisis is extensive and depends on the systems involved, but it should be considered in situations of sepsis, hyperthermia, and altered mental status. Cardiovascular dysfunction, such as atrial tachyarrhythmias and congestive heart failure, includes ischemic heart disease. Hyperpyrexia manifestations include sepsis from pneumonia and malignant hyperthermia, while changes in mental status, such as agitation, delirium, and coma, should be differentiated from psychiatric and cerebrovascular disorders (Akamizu *et al.*, 2012). Recent research highlights the importance of CRP and IL-6 in the search for thyroid storm, as their elevation indicates classic inflammatory processes, aiding in diagnostic accuracy. Additionally, technological innovations, such as the use of artificial intelligence to cross-reference laboratory data and clinical symptoms, promise to improve early diagnosis and prevent future complications. Standardizing diagnostic criteria globally with the best technologies is essential to provide early diagnosis and avoid complications in thyroid storm, ensuring adequate and effective management of the condition.

TREATMENT

Laboratory tests for patients with thyroid storm often show thyroid-stimulating hormone (TSH) levels that are very low or undetectable (<0.01mU/L), elevated free thyroxine (fT4) and/or free triiodothyronine (fT3), and positive thyroid receptor antibody (TRab) if the underlying etiology is Graves› disease (De Almeida; McCalmon; Cabandugama, 2022). Early diagnosis is crucial to initiate aggressive treatment and reduce associated morbidity and mortality (Chiha; Samarasinghe and Kabaker, 2015).

Given the severity of the condition and the potential systemic repercussions such as thermoregulatory dysfunction, tachycardia, congestive heart failure (CHF), hepatic and gastrointestinal manifestations, and central nervous system alterations, all patients should be admitted for intensive treatment. Transfer to an intensive care unit is necessary to halt the damage and achieve a euthyroid state (De Almeida; McCalmon; Cabandugama, 2022). Even with early intervention, mortality remains high, with multiple organ failure being the most common cause, followed by CHF, respiratory failure, cardiac arrhythmias, disseminated intravascular coagulation (DIC), intestinal perforation, and sepsis (Chiha; Samarasinghe and Kabaker, 2015).

Therapeutic efforts aim to contain clinical deterioration, provide symptomatic support, and initiate initial treatment to achieve a euthyroid state before definitive treatment. The use of antithyroid drugs that inhibit hormone synthesis by acting on thyroid peroxidase, such as propylthiouracil (PTU), carbimazole, and methimazole (MMI), is essential. Definitive treatment involves total thyroidectomy or radioactive iodine ablation, depending on the severity of the clinical condition (Chiha; Samarasinghe and Kabaker, 2015).

To achieve a euthyroid state, therapeutic management includes inhibiting the synthesis of new thyroid hormones, inhibiting the release of preformed hormones, and blocking the peripheral effects of excess thyroid hormones. Regarding synthesis inhibition, antithyroid medications like PTU and methimazole are administered orally or via nasogastric tube. The recommended PTU dose is 200 to 250 mg every 4 hours, while the methimazole dose is 20 mg every 4 to 6 hours (Ross, 2023).

To inhibit the release of preformed hormones, inorganic iodine is administered in the form of Lugol›s solution or saturated potassium iodide solution, with a dosage of 8 drops every 6 hours. Patients allergic to iodine can use lithium as an alternative, with a dosage of 300 mg three to four times a day (Ylli; Klubo-Gwiedzinska and Wartofsky, 2019).

In severe or refractory cases, cholestyramine can be used to inhibit the enterohepatic recirculation of thyroid hormones by binding to conjugated products and promoting their excretion. The recommended dose is 1 to 4 g twice a day (Chiha; Samarasinghe and Kabaker, 2015). To control peripheral effects, the beta-blocker propranolol is used. Patients contraindicated for beta-blockers can use short-acting calcium channel antagonists like verapamil (Ylli; Klubo-Gwiedzinska and Wartofsky, 2019).

Glucocorticoids, such as hydrocortisone, are administered to reduce the conversion of T4 to T3, promote vasomotor stability, and treat relative adrenal insufficiency associated with Graves› disease. The recommended dose is 300 mg intravenously, followed by 100 mg every eight hours (Ross, 2023). Supportive therapy includes controlling hyperthermia with acetaminophen and other physical measures, such as cooling blankets and cold fluids. Volume depletion and hypotension, often resulting from fever, vomiting, diarrhea, and sweating, should be treated with intravenous fluid replacement, preferably combined dextrose/saline solution to provide nutritional content and multivitamins (Ylli; Klubo-Gwiedzinska and Wartofsky, 2019).

When thyroid storm is triggered by an infection or when the precipitating factor is unidentified, broad-spectrum antibiotic therapy and a thorough search for infectious foci are considered while awaiting culture results (Ylli; Klubo-Gwiedzinska and Wartofsky, 2019).

Definitive therapy for thyrotoxic crisis is surgical thyroidectomy or treatment with radioactive iodine, essential for preventing recurrences and associated mortality. However, it is crucial that the patient reaches a euthyroid state before any definitive intervention (McGonigle *et al*., 2018).

Therapeutic plasma exchange (TPE) is an option for patients with thyroid storm who do not respond to conventional medical treatment or have contraindications to standard therapies. TPE removes plasma from the blood and replaces it with another fluid, such as albumin or fresh frozen plasma, helping to reduce levels of thyroid hormones, autoantibodies, catecholamines, and cytokines (McGonigle; Tobian; Zink and King, 2017). TPE can effectively restore euthyroidism or improve clinical manifestations of severe thyrotoxicosis. It is especially indicated in refractory thyroid storm cases or to prepare patients for thyroidectomy or other urgent surgeries. Current guidelines recommend using albumin or plasma as replacement fluids during TPE due to their advantages in providing additional binding sites for newly synthesized thyroid hormones. This procedure is a safe and effective treatment option, though limited by cost and the need for specialized resources. It is a valuable option in specific situations where other forms of treatment are contraindicated or insufficient (Montaño; Arrieta and Gonzalez, 2021).

REFERENCES

AKAMIZU, Takashi et al. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. **Thyroid**, v. 22, n. 7, p. 661-679, 2012.

ANGELL, Trevor E. et al. Clinical features and hospital outcomes in thyroid storm: a retrospective cohort study. **The Journal of Clinical Endocrinology & Metabolism**, v. 100, n. 2, p. 451-459, 2015.

BANERJEE, Arnab; BALA, Renu; AGGARWAL, Richa. Atypical presentation of thyroid storm: a diagnostic dilemma. **BMJ Case Reports CP**, v. 12, n. 8, p. e231090, 2019.

BUILES-MONTAÑO, Carlos E. et al. Therapeutic plasmapheresis for the treatment of thyrotoxicosis: A retrospective multi-center study. **Journal of Clinical Apheresis**, v. 36, n. 5, p. 759-765, 2021.

CHIHA, Maguy; SAMARASINGHE, Shanika; KABAKER, Adam S. Thyroid storm: an updated review. **Journal of intensive care medicine**, v. 30, n. 3, p. 131-140, 2015.

DE ALMEIDA, Reuben; MCCALMON, Sean; CABANDUGAMA, Peminda K. Clinical review and update on the management of thyroid storm. **Missouri Medicine**, v. 119, n. 4, p. 366, 2022.

ELENDU, Chukwuka et al. Diagnostic criteria and scoring systems for thyroid storm: An evaluation of their utility–comparative review. **Medicine**, v. 103, n. 13, p. e37396, 2024.

FAROOQI, Samia et al. High risk and low prevalence diseases: Thyroid storm. **American Journal of Emergency Medicine**, v. 69, p. 127-135, 2023.

GALINDO, Rodolfo J. et al. National trends in incidence, mortality, and clinical outcomes of patients hospitalized for thyrotoxicosis with and without thyroid storm in the United States, 2004–2013. **Thyroid**, v. 29, n. 1, p. 36-43, 2019.

IDROSE, Alzamani Mohammad. Acute and emergency care for thyrotoxicosis and thyroid storm. **Acute medicine & surgery**, v. 2, n. 3, p. 147-157, 2015.

MCGONIGLE, Andrea M. et al. Perfect storm: therapeutic plasma exchange for a patient with thyroid storm. **Journal of Clinical Apheresis**, v. 33, n. 1, p. 113-116, 2018.

ROSS, Douglas S. Thyroid storm. **UpToDate**. 2024.

SCHNADIG, Vicki J. Ultrasonography, FNA, mutations, hormones and thyroid nodule obsession in the twenty-first century: a cytopathologist's plea for reason in the age of thyroid storm. **Endocrine**, v. 47, n. 3, p. 664-667, 2014.

YLLI, Dorina; KLUBO-GWIEZDZINSKA, Joanna; WARTOFSKY, Leonard. Thyroid emergencies. **Polish archives of internal medicine**, v. 129, n. 7-8, p. 526, 2019.

Chapter 6

ADRENAL INSUFFICIENCY

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CHAPTER 6

ADRENAL INSUFFICIENCY

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Adrenal insufficiency (AI) is a critical clinical condition characterized by the adrenal cortex›s inability to adequately synthesize or secrete cortisol. This disorder has a prevalence of 82 to 144 cases per million and can be classified as primary, affecting the adrenal glands directly, or secondary and tertiary, resulting from

deficiencies in the stimulation of the pituitary or hypothalamus. Primary adrenal insufficiency (PAI) results from direct adrenal gland failure due to the destruction or damage of the adrenal glands. Common causes include autoimmune adrenalitis, also known as Addison›s disease, and infections such as tuberculosis and HIV (Julie Martin Grace *et al.*, 2020). Secondary adrenal insufficiency (SAI) occurs due to diseases of the pituitary or hypothalamus, such as tumors and their therapies, hypophysitis, or granulomatous infiltration. Tertiary adrenal insufficiency (TAI) is often a consequence of prolonged administration of exogenous glucocorticoids, leading to suppression of the hypothalamic-pituitary-adrenal (HPA) axis (Julie Martin Grace *et al.*, 2020).

Identifying the etiology of adrenal insufficiency is crucial for choosing the appropriate treatment and detecting underlying diseases such as tuberculosis, autoimmune syndromes, or pituitary tumors, which can have significant clinical implications (Lynnette K Nieman *et al.*, 2024). Despite diagnostic advances and the availability of replacement therapies, adrenal crisis (AC) remains a potentially lethal condition that contributes to increased mortality in patients with AI. Failure to administer adequate doses of glucocorticoids during periods of acute stress is one of the main causes of AC, highlighting the need for continuous education for patients and healthcare professionals (Lousada; Mendonça and Bachega, 2021).

AI is associated with increased morbidity and mortality, as well as reduced quality of life for patients, making early diagnosis and appropriate management essential to prevent acute adrenal crises, which can be fatal if not treated adequately (Lousada; Mendonça and Bachega, 2021). The prevalence and incidence of the different forms of AI vary, with Addison›s disease being the most common cause in adults and congenital adrenal hyperplasia (CAH) in children. Population studies indicate high mortality among patients with AI, especially due to adrenal crises (Stefanie *et al.*, 2021).

Adrenal events have an age-related pattern, with respiratory infections being the main trigger in childhood and gastrointestinal infections in older ages. AI has nonspecific symptoms, making early diagnosis and treatment challenging. The main clinical manifestations of an adrenal crisis include hypotension, dehydration, extreme fatigue, nausea, vomiting, abdominal pain, and hypoglycemia. Proper management of adrenal crises requires immediate therapeutic action with intravenous administration of hydrocortisone, fluid infusion, and monitored support (Stefanie *et al.*, 2021).

In recent years, there have been significant advances in understanding and managing AI. New diagnostic techniques, such as the measurement of plasma free cortisol using tandem mass spectrometry, have improved diagnostic accuracy. The introduction of innovative immunological therapies has brought additional challenges in managing adverse effects, such as adrenal insufficiency induced by immune checkpoint inhibitors. Treatment strategies continue to evolve, focusing on personalizing hormone replacement therapy and minimizing risks during intercurrent illnesses. Recent updates also highlight the importance of patient education programs, using questions to guide patients about the importance of

medication use and the use of emergency glucocorticoid injection kits, aiming to improve the early recognition of adrenal crisis symptoms and the appropriate administration of glucocorticoids in emergency situations (Lousada; Mendonça and Bachega, 2021). These trends reinforce the need for a comprehensive understanding of AI, from its physiological bases to the most advanced therapeutic approaches, with the aim of improving clinical outcomes and the quality of life of patients affected by this debilitating condition.

EPIDEMIOLOGY

Acute adrenal insufficiency is more common in patients with primary adrenal insufficiency due to the severity of hypocortisolism and lack of aldosterone. However, it can also occur in secondary adrenal insufficiency. The incidence of adrenal crisis is 5 to 10 per 100 patients per year and accounts for 15 to 40% of deaths related to adrenal insufficiency (Rushworth; Torpy, 2023).

A study found that women are more likely to be hospitalized for adrenal crisis than men (Rushworth; Torpy, 2023). An increased risk of early death has also been observed in younger patients, those under 40 years of age (Stefanie *et al.*, 2021). Primary adrenal insufficiency (PAI) is more common in women, as is adrenal crisis, and is usually diagnosed between the third and fifth decades of life, although it can manifest at any age (Chabre *et al.*, 2017). Specifically, the prevalence of PAI varies geographically, ranging from 1.4 cases per 100,000 in South Africa to 9-22 cases per 100,000 in Europe (Stefanie *et al.*, 2021).

In the 20th century, the main cause of adrenal insufficiency was tuberculosis. However, recent studies have not documented cases of AI resulting from this cause. Conversely, infections remain a leading cause of primary adrenal insufficiency in areas with high rates of tuberculosis, HIV infection, and opportunistic infections such as cytomegalovirus (Stefanie *et al.*, 2021). The increasing prevalence of primary adrenal insufficiency is associated with a rise in cases of autoimmune origin (Chabre *et al.*, 2017).

Adrenal crisis can occur in patients with undiagnosed or inadequately treated chronic adrenal insufficiency, or when corticosteroid administration is abruptly stopped. The incidence of this pathology can increase with the use of low-dose, short-duration glucocorticoids. Additionally, initiating L-thyroxine therapy in patients with thyroid disease and the development of hyperthyroidism due to Graves› disease can trigger a crisis due to faster inactivation of cortisol than in individuals without thyroid disease (Stefanie *et al.*, 2021).

Primary adrenal insufficiency is mainly caused by autoimmunity, which is the most common cause in adults. It can also be associated with factors such as tuberculosis, HIV, or fungal infections that can damage the adrenal glands. In children, congenital adrenal hyperplasia prevails, while hereditary conditions such as adrenoleukodystrophy are also relevant. Secondary adrenal insufficiency is related to prolonged use of

exogenous corticosteroids in high doses and for long periods, which can suppress ACTH (adrenocorticotropic hormone) production by the pituitary gland, being twice as prevalent as primary insufficiency. The prevalence of primary adrenal insufficiency is rare, affecting 10-20 people per 100,000 population. In industrialized countries like Iceland, the prevalence of Addison›s disease has increased from 3.9 cases per 100,000 in 1968 to 22 cases per 100,000 in 2016 (Stefanie *et al.*, 2021).

There is a clear geographical difference in the prevalence of Addison›s disease. In underdeveloped countries such as South Africa, the prevalence is 1.4 cases per 100,000 population. In contrast, in developed countries like those in Europe, the prevalence increases to 9 to 22 cases per 100,000 population. The prevalence of congenital adrenal hyperplasia varies according to the population, being approximately 0.5 to 1 person per 10,000 inhabitants (Stefanie *et al.*, 2021). Secondary adrenal insufficiency is more prevalent than primary, with 42 cases per 100,000 European inhabitants.

Adrenal crisis accounts for 15 to 40% of reported deaths from adrenal insufficiency. Each year, 5 to 10 patients per 100 population suffer adrenal crises, being more prevalent in those previously diagnosed with PAI. The mortality from adrenal crises is low, at 0.5 patients per 100 population per year. The mortality from adrenal emergencies is lower, being below 1% of cases after hospital admission (Stefanie *et al.*, 2021).

DIAGNOSIS

The identification of adrenal insufficiency (AI) involves both clinical analysis and consideration of the patient›s social and financial circumstances. In addition to facing higher risks of morbidity and mortality due to adrenal crises, these patients are subject to other medical disorders such as autoimmune syndromes, infectious conditions, and congenital deficiencies responsible for the adrenal insufficiency itself. This concern justifies the importance of early and swift diagnostic investigation (He; Findling and Auchus, 2018).

Moreover, the management of the disease depends on diagnostic clarification since adrenal insufficiency has various etiologies that differ in clinical and therapeutic approaches. Currently, the prevalence of secondary and tertiary adrenal insufficiencies is significantly higher compared to primary adrenal insufficiency (PAI), whose investigation relies on specific and dynamic methods such as clinical manipulation of the patient. This underscores the essential role of clinical and complementary analysis in managing this disease (He; Findling and Auchus, 2018).

The symptomatology of AI is quite diverse, presenting with nonspecific symptoms such as nausea, vomiting, and fatigue, mimicking other diseases, or manifesting as a catastrophic adrenal crisis, evolving with circulatory shock and coma. Therefore, a detailed medical history, medication history, high suspicion, and appropriate laboratory evaluation are of utmost importance (Shaikh *et al.*, 2023).

Furthermore, the clinical presentation helps differentiate the multiple etiologies responsible for acute adrenal insufficiency. PAI is accompanied by typical symptomatic characteristics resulting from glucocorticoid and mineralocorticoid deficiency, such as fatigue, salt craving, nausea, loss of appetite, weight loss, myalgia, and abdominal pain. In contrast, secondary (SAI) and tertiary (TAI) dysfunctions exhibit symptoms restricted to the mass effect of a hypothalamic-pituitary lesion, such as headache, visual field defects, galactorrhea, and even amenorrhea (Martin-Grace *et al.*, 2020).

In AI induced by glucocorticoids, patients may present with skin pallor due to alterations in the melanocortin 1 receptor located in the skin by ACTH, leading to decreased activation (Pelewicz; Miskiewicz, 2021). Hyperpigmentation observed during physical examination is prominent in regions such as skin folds, areolas, and palmar creases, and may also involve the oral mucosa and gums (Charoensri; Auchus, 2024). In PAI, androgen deficiency in women can result in decreased body hair and reduced libido, as androgens produced by the adrenals constitute a significant portion of the total body amount in women. In contrast, in men, the primary source of androgens responsible for body hair is the testes, not the adrenals (Charoensri; Auchus, 2024).

However, the nonspecific nature of adrenal insufficiency symptoms contributes to delayed diagnostic elucidation and increases medical diagnostic errors, with about 68% of patients leaving consultations with gastrointestinal or psychiatric suppositions. For these reasons, it is determined that investigation should never delay the immediate treatment of an acute condition, which is done with the use of parenteral hydrocortisone (Martin-Grace *et al.*, 2020).

Laboratory methods can be used to differentiate AI and its various etiologies. The main alterations are found through routine tests such as a complete blood count and electrolytes. In primary AI, a specific hydroelectrolytic alteration is hyperkalemia. A biochemical alteration frequently found in all types of AI is hyponatremia. This results from a physiological phenomenon due to cortisol deficiency, resulting in the inability to suppress arginine vasopressin in the hypothalamus. Thus, the kidneys› ability to excrete free water is compromised, leading to greater water retention despite decreased plasma osmolality. The lack of aldosterone also contributes to hypovolemic hyponatremia in primary adrenal insufficiency, resulting from renal loss of water and sodium, along with prerenal azotemia. Additionally, in primary and central AI, occasional laboratory analyses may show normocytic anemia, eosinophilia, lymphopenia, and hypercalcemia (Charoensri; Auchus, 2024).

If there is clinical suspicion of AI, it is extremely important to conduct diagnostic investigation. However, this should never delay the initiation of glucocorticoid treatment. Knowledge of physiology is essential for early diagnosis and understanding of screening tests. A commonly used screening method in clinical practice is the measurement of basal serum cortisol. Its secretion follows the circadian cycle, peaking between 6 am and 9 am. Therefore, a reference time interval for collection has been established, specifically between

8-9 am. External factors such as pregnancy, inflammation, and critical illnesses should be considered as they can alter the results, as 90% of cortisol is bound to CBG (Pelewicz; Miskiewicz, 2021).

If basal serum cortisol levels are below 4 μg/dL (110 nmol/L) along with plasma ACTH above the normal reference (>100 pg/mL), the diagnosis of primary adrenal insufficiency can be confirmed without dynamic tests. Conversely, diagnosing central adrenal insufficiency is more complex than primary due to the lack of dynamic tests in most published diagnostic criteria studies. Generally, when morning serum cortisol is below 4 μg/dL and plasma ACTH is below or near the lower limit of the normal range (typically <10 pg/mL), it may suggest some degree of central adrenal insufficiency (Charoensri; Auchus, 2024). However, it is important to remember that cortisol-binding globulin deficiency, glucocorticoid resistance, and hypersensitivity can affect adrenocortical function tests (Bornstein *et al*., 2016).

Certain conditions can predispose patients to primary adrenal insufficiency, including autoimmune diseases such as type 1 diabetes, autoimmune gastritis, pernicious anemia, and vitiligo, as well as infectious diseases like tuberculosis, HIV, cytomegalovirus, candidiasis, and histoplasmosis. Additionally, inhibitors of adrenal enzymes and medications that act on the central nervous system, such as phenytoin and carbamazepine, can induce PAI by increasing cortisol metabolism. Therefore, if the patient is taking these medications, the diagnostic threshold should be kept low (Bornstein *et al*., 2016).

Diagnostic tests for AI include the synthetic ACTH stimulation test (SST), insulin tolerance test (ITT), metyrapone stimulation test, glucagon stimulation test, and also CRH stimulation (Pelewicz; Miskiewicz, 2021). The insulin tolerance test has been considered the reference method for diagnosing forms of adrenal insufficiency, particularly when central causes are suspected, whether they stem from hypothalamic or pituitary dysfunctions, as the corticotropin stimulation test can produce falsely negative results. In this test, an intravenous bolus of insulin (0.1 IU/kg) is administered to induce severe hypoglycemia, activating a counter-regulatory response and evaluating the entire HPA axis. The lowest blood glucose level occurs between 30 to 45 minutes after insulin administration, with the criterion for central adrenal insufficiency being a peak serum cortisol level below 18 μg/dL (500 nmol/L) at 60 to 90 minutes (Charoensri; Auchus, 2024).

Despite ITT being the gold standard for secondary adrenal insufficiency, it is possible to observe risks for patients, requiring a high level of supervision and being contraindicated for those with a history of cardiovascular disease or seizures. Additionally, reference values have not been established for modern cortisol assays. Consequently, it has been less used in clinical practice (Charoensri; Auchus, 2024). Metyrapone stimulation tests, glucagon stimulation tests, and CRH stimulation are used less frequently and lack sufficient investigation, although they are useful in evaluating ACTH axis function and are highly valuable for diagnosing glucocorticoid-induced AI (Pelewicz; Miskiewicz, 2021).

The corticotropin stimulation method is used for confirming the diagnosis of PAI. Two synthetic corticotropin analogs can be used: cosyntropin (Cortrosyn, Amphastar, etc.) and tetracosactrin (Synacthen, Novartis Pharma, etc.). Both have the same dose of 250 μg administered parenterally (IV or IM). This dose is considered standard for practicality and is recommended by the Endocrine Society›s clinical practice guideline. Serum cortisol levels are measured 30-60 minutes after administration to assess the peak cortisol level. In primary AI, 30-minute dosing diagnosed 95% of cases with high accuracy. In central AI, 60-minute post-injection dosing showed better diagnostic accuracy. This method can be used in patients suspected of adrenal crisis, with morning serum cortisol <140 nmol/L and plasma ACTH >2 times the normal value or >66 pmol/L. This finding is highly predictive of PAI. In healthy individuals, a peak cortisol concentration >500 nmol/L is expected, suggesting AI in those where the peak cortisol remains <500 nmol/L (the cutoff value may vary depending on the assay used), as the zona fasciculata is already being excessively stimulated by the elevated level of endogenous ACTH. Additionally, the adrenal cortex is replaced by fibrous tissue (Younes; Bourdeau and Lacroix, 2021).

Finally, basal morning cortisol is used as a first-line investigation for SAI/TAI. Levels <3 μg/dL (83 nmol/L) indicate AI, and levels >15 μg/dL (413 nmol/L) exclude the diagnosis. Given this etiological origin, the pituitary profile type is identified by requesting laboratory tests for prolactin, LH, FSH, TSH, Free T4, estradiol, testosterone, and insulin-like growth factor (IGF-1). Simultaneous measurement of renin and aldosterone is also requested to confirm mineralocorticoid deficiency (Younes; Bourdeau and Lacroix, 2021).

After confirming primary adrenal insufficiency, anti-adrenal antibodies, including 21-hydroxylase antibodies (routinely assessed to rule out autoimmunity), screening for tuberculosis exposure in endemic areas, and cross-sectional imaging, such as MRI of the adrenal glands, are proposed to exclude infectious, hemorrhagic, and neoplastic etiologies (Shaikh et al., 2023). In some situations, standard tests may not be reliable. Patients with abnormalities in cortisol-binding globulin (CBG) or albumin, women using oral contraceptives (high CBG), or those with cirrhosis or nephrotic syndrome (low CBG) may have cortisol thresholds leading to misdiagnosis (De Miguel Novoa *et al.*, 2014).

If CBG is high, as in scenarios of oral contraceptive use or pregnancy, CBG measurement should be performed. If levels are normal, usual tests can be conducted. If CBG is elevated, morning serum cortisol should be measured (De Miguel Novoa *et al.*, 2014).

The metyrapone test is one possible alternative to ITT for evaluating HPA axis function. Metyrapone can inhibit the enzyme 11β-hydroxylase and, when administered at night, prevents the normal morning cortisol rise, increasing ACTH and steroid precursor secretion. For adequate inhibition of 11β-hydroxylase, a serum cortisol level below 5 μg/dL is required. If there is an increase in plasma 11-deoxycortisol, it may indicate an intact HPA axis. However, metyrapone has limited availability due to high cost and heterogeneity

of 11-deoxycortisol assays, restricting its widespread use. Additionally, it may precipitate an adrenal crisis in symptomatic patients (Charoensri; Auchus, 2024).

Non-invasive tests are also available, such as basal and stimulated salivary cortisol testing, which is currently being explored as an approach for diagnosing AI. Studies have shown that salivary cortisol values after cosyntropin stimulation are comparable to serum cortisol. Salivary cortisol is a highly promising test, especially in pediatrics, as it is simple, non-invasive, and easy to administer (Charoensri; Auchus, 2024).

A recent retrospective study with 370 patients in Spain highlighted the importance of considering sex-specific and test-type-specific cutoff values when interpreting the corticotropin test. This is necessary to minimize false-positive results and improve specificity. Both the corticotropin stimulation test and the metyrapone test, commonly used to diagnose central adrenal insufficiency, cannot replace the insulin tolerance test (gold standard for evaluating the HPA axis) (Younes; Bourdeau and Lacroix, 2021).

TREATMENT

The treatment of adrenal insufficiency initially involves intervention aimed at stabilizing the patient, achieving optimal management to replace adrenal hormones to mimic physiological secretion, thereby maintaining the patient›s quality of life without the adverse effects of excessive medication. Therefore, the goal in treating AI is hormone replacement, such as glucocorticoids and mineralocorticoids, correcting electrolytes, providing hemodynamic support, and managing any adverse effects (Charoensri; Auchus, 2024; De Miguel Novoa *et al.*, 2014; Nieman; Lacroix and Martin, 2012). The treatment regimen varies according to the etiology of AI; in cases of primary AI, full doses of glucocorticoids and mineralocorticoids should be replaced, whereas in central AI (secondary or tertiary), the glucocorticoid dose can be lower, without mineralocorticoids, as the patient still preserves part of the hormone secretion (Charoensri; Auchus, 2024; Bornstein *et al.*, 2016; De Miguel Novoa *et al.*, 2014; Nieman; Lacroix and Martin, 2012). Moreover, the etiology also determines the duration of treatment; primary AI requires lifelong replacement, while secondary or tertiary AI may also require lifelong treatment but is expected to be more prolonged (Kumar; Wassif, 2022).

The management of the disease also includes continuous monitoring and patient education regarding «sick day rules,» to teach them to understand the signs of AI and that glucocorticoid replacement must always be adjusted to daily needs and stressful situations, such as surgical or invasive procedures (Simpson et al., 2020). Patients should also understand that excess medication can cause signs and symptoms characteristic of Cushing›s syndrome, while a lack of hormones can be fatal (Nieman; Lacroix and Martin, 2012).

The value of random cortisol measurement is considered a good marker of hypothalamic-pituitary-adrenal (HPA) axis activity and is directly proportional to the degree

of stress. However, randomized studies have not shown a minimum plasma cortisol level below which mortality increases in critical illnesses (Hamrahian & Fleseriu, 2017). Factors affecting plasma cortisol levels in sick patients include gender, type and duration of illness, patient volume status, differences in cortisol assays, levels of corticosteroid-binding globulins (CBG), glucocorticoid (GC) polymorphisms, different activities of ACTH, CRH, and 11-hydroxysteroid dehydrogenase enzyme subtypes (Hamrahian; Fleseriu, 2017).

Additionally, in patients with vasopressor- and fluid-refractory septic shock, glucocorticoids (GCs) may be used as standard treatment regardless of serum cortisol levels, as the benefit of GC therapy for patients may not be associated with AI. The most recent consensus on severe sepsis and septic shock recommends hydrocortisone therapy regardless of serum cortisol concentrations if hemodynamic instability is refractory to adequate volume resuscitation and vasopressor therapy (Hamrahian; Fleseriu, 2017).

Moreover, a brief trial of hydrocortisone treatment in critically ill patients with hemodynamic instability without septic shock but with borderline serum cortisol levels (10-15 μg/dL) may be reasonable as long as treatment is discontinued in the absence of any significant response to avoid harm (Hamrahian; Fleseriu, 2017).

After various studies, random cortisol and free cortisol measurements were recommended as the primary methods for evaluating adrenal function in critically ill patients. The cosyntropin stimulation test (CST) should not be used to define relative adrenal insufficiency (RAI) in critically ill patients. However, in patients without septic shock and with borderline random cortisol levels, performing the CST may be reasonable (Hamrahian; Fleseriu, 2017). A free cortisol level ≥ 1.8 mcg/dL was proposed as a criterion for normal adrenal function in critically ill patients without septic shock. However, more outcome-based studies are needed to validate free cortisol cutoff points in critically ill patients (Hamrahian; Fleseriu, 2017).

The ideal glucocorticoid replacement should mimic physiological secretion, be easy to administer and control, and have low metabolic variability. However, this is not always possible (De Miguel Novoa *et al.*, 2014). Hydrocortisone is the drug of choice as it has both glucocorticoid and mineralocorticoid effects. Its administration is recommended in doses of 15-25 mg/day, divided into two or three times a day to simulate the circadian rhythm of cortisol (Charoensri; Auchus, 2024; Kumar; Wassif, 2022; Nieman; Lacroix and Martin, 2012; Nowotny *et al.*, 2021). For emergency situations, the recommended dose is 100 mg intramuscularly (Charoensri; Auchus, 2024; Kumar; Wassif, 2022; Simpson *et al.*, 2020; Bornstein *et al.*, 2016; Nowotny *et al.*, 2021).

Hydrocortisone has good bioavailability and a short half-life, but dose division and adjustment can be difficult (De Miguel Novoa et al., 2014). Long-acting glucocorticoids, such as prednisolone and dexamethasone, are not as recommended due to their long half-life and unfavorable nocturnal glucocorticoid activity. Prednisolone can be used in doses of 3-5 mg/day for better adherence and control (Nieman; Lacroix and Martin, 2012; Bornstein

et al., 2016; Charoensri; Auchus, 2024), but it can cause dyslipidemias, osteopenia, and osteoporosis (Charoensri; Auchus, 2024). Dexamethasone, although long-lasting, is not recommended due to the risk of Cushing›s syndrome and difficulty in titration (Nieman; Lacroix and Martin, 2012).

Patients with gastrointestinal disease or after major surgeries should receive parenteral glucocorticoids (Charoensri; Auchus, 2024; Bornstein *et al.*, 2016). Prednisone and dexamethasone should be used in patients with poor adherence to multiple doses due to metabolic variability and risk of intoxication (De Miguel Novoa *et al.*, 2014). Patients under treatment should be evaluated quarterly during dose titration and annually thereafter, including blood pressure measurement, heart rate, weight gain or loss, signs of lethargy or impaired sleep, and Cushingoid signs (Nieman, Lacroix; Martin, 2012; De Miguel Novoa *et al.*, 2014). Adequate glucocorticoid replacement control is achieved through clinical evaluation or cortisol curve (Kumar; Wassif, 2022). Patient education on «sick day rules» is essential to adjust the dose, such as doubling the dose when necessary or associating a fast-acting glucocorticoid during stress (Simpson *et al.*, 2020).

Patients on long-term supraphysiological glucocorticoid replacement are at higher risk of infections, increased hospitalization rates, and antimicrobial use due to the immunosuppressive activity of glucocorticoids. In women with primary adrenal insufficiency (PAI), high doses of glucocorticoids increase the risk of ischemic and cardiovascular heart disease, as well as compromise sleep quality (Nowotny *et al.*, 2021).

For primary adrenal insufficiency, it is necessary to associate mineralocorticoids from diagnosis to maintain volume levels, normal blood pressure, electrolyte balance, and reduce salt cravings. The drug of choice is fludrocortisone (FC), which mimics natural aldosterone secretion and should be administered in morning doses of 0.05 to 0.20 mg/day (Bornstein *et al.*, 2016; Kumar; Wassif, 2022; Charoensri; Auchus, 2024). The initial dose can be 0.05 to 0.1 mg/day, especially for patients on hydrocortisone or cortisone acetate (Nieman; Lacroix and Martin, 2012). The dose should be temporarily adjusted in hot climates and excessive sweating or stressful situations (Nieman; Lacroix and Martin, 2012; Bornstein *et al.*, 2016; Kumar; Wassif, 2022; Charoensri; Auchus, 2024; De Miguel Novoa *et al.*, 2014).

Treatment options also include gene therapy and the potential to restore the defect in certain forms of monogenic primary adrenal insufficiency (PAI); adrenal cortical transplantation, a promising area already with successful reports in the literature; and new cell replacement and encapsulation technologies, which may even achieve the cure of primary adrenal insufficiency with the restoration of hypothalamic-pituitary-adrenal (HPA) axis function. Stem cells offer the potential to regenerate adrenal cortical tissue in patients with AI, and this is currently an area of intense research (Kumar; Wassif, 2022; Bornstein *et al.*, 2016).

Finally, treatment options to reverse autoimmune adrenal insufficiency have been developed, which include B-lymphocyte-depleting immunotherapy with rituximab, regular

therapy with subcutaneous tetracosactide (ACTH1-24), and dual therapy with rituximab and repeated depot tetracosactide (Kumar; Wassif, 2022). More recent studies have reported a successful mother-to-daughter allograft in a pediatric patient who developed adrenal insufficiency after acquiring fulminant meningococcemia. However, these multi-organ transplants are only viable and/or indicated when recipients have severe comorbidities (Babot *et al*., 2015). A study conducted by Hornsby et al. demonstrated that the transplantation of human adrenal cortical cells into mice with severe combined immunodeficiency and adrenalectomy could be an effective technique for treating adrenal insufficiency (Babot *et al*., 2015).

REFERENCES

BORNSTEIN, Stefan R. et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. **The Journal of Clinical Endocrinology & Metabolism**, v. 101, n. 2, p. 364-389, 2016.

CHABRE, Olivier et al. Group 1. Epidemiology of primary and secondary adrenal insufficiency: prevalence and incidence, acute adrenal insufficiency, long-term morbidity and mortality. In: Annales d›endocrinologie. **Elsevier Masson**, 2017. p. 490-494.

CHAROENSRI, Suranut; AUCHUS, Richard J. A Contemporary Approach to the Diagnosis and Management of Adrenal Insufficiency. **Endocrinology and Metabolism**, v. 39, n. 1, p. 73, 2024.

DE NOVOA, Paz et al. Guidelines for diagnosis and treatment of adrenal insufficiency in adults. **Endocrinología y Nutrición (English Edition)**, v. 61, p. 1-34, 2014.

HAMRAHIAN, Amir H. et al. Evaluation and management of adrenal insufficiency in critically ill patients: disease state review. **Endocrine Practice**, v. 23, n. 6, p. 716-725, 2017.

HE, Xin; FINDLING, James W.; AUCHUS, Richard J. Diagnosis and management of adrenal insufficiency. **Adrenal Disorders: Physiology, Pathophysiology and Treatment**, p. 199-215, 2018.

KUMAR, Rajeev; WASSIF, W. S. Adrenal insufficiency. **Journal of Clinical Pathology,** v. 75, n. 7, p. 435-442, 2022.

LOUSADA, Lia Mesquita; MENDONCA, Berenice B.; BACHEGA, Tania ASS. Adrenal crisis and mortality rate in adrenal insufficiency and congenital adrenal hyperplasia. **Archives of endocrinology and metabolism**, v. 65, p. 488-494, 2021.

MARTIN-GRACE, Julie et al. Adrenal insufficiency: physiology, clinical presentation and diagnostic challenges. **Clinica chimica acta**, v. 505, p. 78-91, 2020.

NIEMAN, L.; LACROIX, Andre; MARTIN, K. Treatment of adrenal insufficiency in adults. **UpToDate**, 2012.

NIEMAN, Lynnette K.; LACROIX, Andre; MARTIN, K. Clinical manifestations of adrenal insufficiency in adults. UpToDate. Waltham, MA: **UpToDate**. https://www. uptodate. com/contents/clinical-manifestations-ofadrenal-insufficiency-in-adults. Last updated November, v. 4, 2016.

NIEMAN, Lynnette K; DESANTIS, Anthony. Determining the etiology of adrenal insufficiency in adults. **UpToDate**. 2024.

NOWOTNY, Hanna et al. Therapy options for adrenal insufficiency and recommendations for the management of adrenal crisis**. Endocrine**, v. 71, p. 586-594, 2021.

PELEWICZ, Katarzyna; MIŚKIEWICZ, Piotr. Glucocorticoid withdrawal—an overview on when and how to diagnose adrenal insufficiency in clinical practice. **Diagnostics**, v. 11, n. 4, p. 728, 2021.

RUIZ-BABOT, Gerard et al. New directions for the treatment of adrenal insufficiency. **Frontiers in endocrinology**, v. 6, p. 141252, 2015.

RUSHWORTH, R. Louise; TORPY, David J. The changing epidemiology of adrenal insufficiency: iatrogenic factors predominate. **Journal of the Endocrine Society**, v. 7, n. 3, p. bvad017, 2023.

SHAIKH, Salomi et al. Adrenal failure: an evidence-based diagnostic approach. **Diagnostics,** v. 13, n. 10, p. 1812, 2023.

SIMPSON, Helen et al. Guidance for the prevention and emergency management of adult patients with adrenal insufficiency. **Clinical Medicine**, v. 20, n. 4, p. 371, 2020.

STEFANIE, Hahner et al. Adrenal insufficiency (Primer). **Nature Reviews: Disease Primers**, v. 7, n. 1, 2021.

YOUNES, Nada; BOURDEAU, Isabelle; LACROIX, Andre. Latent adrenal insufficiency: from concept to diagnosis. **Frontiers in Endocrinology**, v. 12, p. 720769, 2021.

Chapter 7

SEPSIS

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CHAPTER 7

SEPSIS

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Sepsis is a physiological and biochemical dysfunction resulting from an infection, usually bacterial (Huang; Cai and Su, 2019; Hunt, 2024). Its complex pathogenesis involves immunological changes, autophagy, an unbalanced inflammatory response, coagulopathy, and neuroendocrine abnormalities (Huang; Cai and Su, 2019). Lack of early diagnosis and treatment can lead to septic shock, organ failure, and death (Karampela; Fragkou, 2022).

Although sepsis treatment has advanced, incidence and mortality continue to rise, with over 30 million cases annually worldwide, making it a leading cause of death in critically ill patients. Advances in treatment have reduced organ failure, but permanent immunological dysfunction has become the main cause of death in advanced sepsis (Huang; Cai and Su, 2019). The heterogeneity of patients, varying by etiology and severity, remains a challenge for sepsis management and diagnosis, with no reliable tests available in emergencies (Huang; Cai and Su, 2019; Hunt, 2024).

Sepsis affects 1-2% of hospitalized patients, with hospital mortality around 27%, increasing to 42% in intensive care units. Hospital-acquired infections account for up to a quarter of cases, with substantial economic costs, reaching about $23.6 billion in the US in 2013, with an annual growth rate of 11.5% (Huang; Cai and Su, 2019; László *et al.*, 2015).

Diagnostic criteria differ inside and outside the ICU. In the ICU, a SOFA score of 2 points in patients with infection suggests sepsis. Outside the ICU, the presence of two or more qSOFA criteria is used. Biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), TNF-α, IL-6, MCP-1, and miRNA are essential for early diagnosis (Karampela; Fragkou, 2022; Hunt, 2024). Sepsis involves dysfunctions in multiple organs, making clinical diagnosis challenging (Karampela; Fragkou, 2022; Hunt, 2024).

Treatment for sepsis includes antibiotics, antivirals, and vasoactive agents, although there are no FDA-approved specific therapies. Research focuses on modulating the inflammatory response, coagulopathy, and immunological dysfunction. In the early stages, excessive inflammatory response is critical, while in advanced sepsis, persistent immunological dysfunction predominates (László *et al.*, 2015; Hunt, 2024).

Biomarkers like PCT and CRP are widely used in sepsis diagnosis and treatment guidance but face challenges of sensitivity and specificity (Huang; Cai and Su, 2019). New alternatives, such as regulating the inflammatory response, are being explored. Corticosteroids, anti-cytokine agents, and kinase inhibitors can be used to suppress hyperinflammation in sepsis (Karampela; Fragkou, 2022).

Advances in bioinformatics and artificial intelligence show promising results in developing new diagnostic tools. Short-acting β-blockers and blood purification techniques have shown potential as complementary therapies. The SOFA score, which combines clinical signs and biomarkers of organ dysfunction, is an important diagnostic criterion (Karampela; Fragkou, 2022).

Classifying sepsis into distinct categories can facilitate the identification of more specific treatments. Sensitive and specific laboratory tests are needed to rapidly detect the onset and extent of the inflammatory response and monitor disease progression. However, the role of a well-trained and experienced physician remains irreplaceable (László *et al.*, 2015).

EPIDEMIOLOGY

Initiatives to improve the epidemiological understanding of sepsis are essential. For this, sepsis must be included in national research and healthcare agendas, with increased resources for research and programs (Cassini *et al.*, 2021). According to the Global Burden of Sepsis study, 31.5% of sepsis survivors who previously did not require care now present this need, increasing the life risk for such patients. Mortality within 12 months after discharge was 30.7% (Fleischmann-Struzek and Rudd, 2023). The global burden of sepsis in 2020 was estimated at 48.9 million incident cases, with a rate of 677.5 cases per 100,000 inhabitants. However, despite the increase in studies on sepsis incidence, calculating this measure at a global level remains a challenge (Fleischmann-Struzek and Rudd, 2023).

The mortality rate of sepsis and septic shock ranges between 30% and 50%, depending on factors such as race, gender, age, and organ impairment. Male, elderly, and immunocompromised patients are more likely to develop these conditions. In children, sepsis may be linked to genetic inheritance (Pandey, 2024).

The incidence of sepsis and septic shock grows by 9% annually (Martin *et al.*, 2003). The anatomical site of infection significantly impacts the sepsis mortality rate. Lower respiratory and biliary tract infections and intra-abdominal infections are associated with higher lethality, while skin and musculoskeletal infections show lower mortality rates. Lower respiratory tract infection was the leading cause of death, followed by genitourinary tract infections and systemic fungal infections. The incidence of these infections has shown a sharp increase, especially musculoskeletal and skin infections (Chou *et al.*, 2020).

Higher prevalence and hospital mortality rates are observed in low- and middle-income countries (LMICs). Maternal sepsis is one of the leading causes of sepsis incidence and mortality globally. During the COVID-19 pandemic, the incidence of non-virus-related sepsis decreased due to the reduction in other respiratory infections and post-surgical sepsis. Interventions such as pneumococcal pneumonia vaccination and ventilator-associated bundles have been used to prevent infections. Assessing the impact of the infection site is crucial for better treatment. Hospital mortality is higher in patients with intra-abdominal infection and lower in cases of primary bacteremia (Pandey, 2024).

Risk factors for sepsis include diabetes, malignancy, chronic kidney and liver disease, corticosteroid use, burns, major surgery, trauma, permanent catheters, prolonged hospitalization, hemodialysis, and extremes of age. Nutritional assessment is relevant, with critically ill patients needing 25 to 30 kg to meet protein needs (Huang et al.). Markers such as SDMA (Symmetrical Dimethylarginine) and ADMA (Asymmetrical Dimethylarginine) are high-risk combinations for sepsis survival (Winkler *et al.*, 2024). Furthermore, studies show that pre-existing comorbidities increase the risk of adverse outcomes after sepsis, highlighting the importance of recognizing these high-risk populations (age, underlying diseases, and vulnerable groups) (Pandey, 2024).

DIAGNOSIS

Sepsis triggers a systemic inflammatory response that can lead to multiple organ failure. Early signs include fever, tachycardia, tachypnea, and leukopenia. Severe sepsis could be indicated by hypoxia, hypotension, cyanosis, brain dysfunction, oliguria, and paralytic ileus and may progress to septic shock (Pandey, 2024). The most accepted definition by the 45th Critical Care Medicine Society defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection. The qSOFA and SOFA scores are used for assessment, with a positive diagnosis for sepsis if the qSOFA is greater than two points or the SOFA reaches two points. However, these scores are criticized for low specificity and the possibility of delaying the diagnosis and treatment of severe infections (Pant; Mackraj and Govender, 2021).

The early diagnosis of sepsis is crucial for patient prognosis and reducing mortality, typically achieved through blood cultures and molecular tests. However, it is hindered by the absence of well-established signs and symptoms, and the lack of a technical standard that unanimously confirms the diagnosis (Pant; Mackraj and Govender, 2021). Early identification of the worsening condition and the genesis of the infection is essential. Unfortunately, conventional indicators like fever and leukocytosis, as well as new biomarkers, are not sufficiently sensitive or specific to cover the variability of the pathobiology of different patients. Thus, it is unlikely that a single diagnostic parameter will be sufficient; using multiple tests is more reliable (Molnár *et al.*, 2016).

The lack of a rapid and precise test for the identification of sepsis complicates the correct diagnosis, often challenging healthcare professionals. This can result in overtreatment with antibiotics «just-in-case,» inadequate or delayed diagnoses, and failure to recognize non-infectious conditions. Sepsis-3 attempts to standardize terminology to avoid the inappropriate use of terms, as not every infection results in sepsis (Tidswell; Inada-Kim and Singer, 2021). A retrospective review of 369 patients with suspected infection revealed that only 22% met the sepsis criteria after independent evaluation, highlighting inconsistencies in current diagnoses and coding (Tidswell; Inada-Kim and Singer, 2021). This inconsistency compromises the accurate epidemiology of sepsis, making it difficult to understand the extent of the problem and evaluate new treatment and diagnostic strategies. Applying levels of certainty to the diagnosis is recommended to increase the accuracy of records and improve clinical care (Tidswell; Inada-Kim and Singer, 2021).

The microbiological diagnosis of sepsis is often carried out by blood culture, preferably before starting antibiotic treatment, with the collection of 2 to 3 sets to identify the origin and etiological agent of the infection. This process requires optimization of the pre-analytical, analytical, and post-analytical stages (Escartín; Martínez-López and Nadal-Barón, 2023). Although standard blood culture techniques are excellent for identifying and isolating microorganisms, they have disadvantages such as long response times, which can

take up to 5 days for pathogen growth, plus an additional 48 hours for antibiotic susceptibility testing. Furthermore, they have low sensitivity, requiring a large sample volume, with up to 63% of cases potentially resulting in false negatives after treatment initiation, and are subject to pre-analytical variables (Lippi, 2019).

Pre-analytical measures include proper sample collection, encompassing skin sterilization, blood volume collected, number of samples, incubation time of the bottles, and transport to the laboratory, all crucial factors for diagnostic time and quality (Escartí; Martínez-López and Nadal-Barón, 2023). In addition to blood cultures, some hospitals adopt standards for requesting laboratory tests, including complete blood count, basic biochemistry, coagulation study, acid-base balance, urine, and biomarkers, which generate alerts for rapid control of samples. Analytical processes involve the rapid processing of bottles flagged as positive and the use of rapid identification and antimicrobial susceptibility testing methods, including molecular diagnostics, rapid diagnostics, and gram tests, important for detecting microorganisms and resistance genes in 30 minutes to 5 hours (Escartín; Martínez-López and Nadal-Barón, 2023).

The T2 magnetic resonance technique stands out, using paramagnetic nanoparticle sensors to detect bacteria and yeast in the blood with high sensitivity (>95%) and low cell concentration (1 cell/ml), though it faces interpretation challenges compared to traditional tests (Escartín; Martínez-López and Nadal-Barón, 2023). Rapid methods monitor bacterial growth in response to antibiotics using techniques like nephelometry, PNA FISH with morphokinetic cell analysis, microfluidics with fluorescence microscopy, microscopy imaging, volatile emission matrix detection, and flow cytometry (Escartín; Martínez-López and Nadal-Barón, 2023).

Post-analytical actions depend on joint medical, hospital, and laboratory evaluation, analyzing the patient›s clinical context, test results, and necessary therapeutic measures (Escartín; Martínez-López and Nadal-Barón, 2023). Various screening tools, such as early warning signs and the Rothman Index, are used to rapidly detect sepsis, even in the pre-hospital phase. The Surviving Sepsis Campaign (SSC) lists screening and diagnostic tools, considering clinical parameters such as heart rate, respiratory rate, temperature, blood pressure, oxygen saturation, lactate, urea, C-reactive protein, complete blood count, blood cultures, urine cultures, and cultures of other body fluids. Imaging techniques are also useful for confirming the condition (Pandey, 2024).

Given the various diagnostic difficulties, several scoring systems have been developed to assess sepsis severity and predict outcomes. Initially, the definition of sepsis depended on the Systemic Inflammatory Response Syndrome (SIRS) criteria. However, this approach was questioned for its lack of clinical specificity. Currently, the definition of sepsis is based on the objective presence of acute dysfunction indicating an inadequate host response to infection. The evolution of risk stratification strategies offers better opportunities for early detection of sepsis (Laura *et al.*, 2020).

Alerts are essential components of systems designed to draw healthcare professionals› attention to critical information when certain parameters are exceeded. These help in continuous monitoring of changes in the patient›s condition, facilitating timely interventions. However, the dispersion of information can hinder the detection of changes and result in ineffective care. With technological advancement, machine learning (ML) algorithms have been developed to improve early diagnosis and management of sepsis, even with established institutional protocols. ML enables computers to learn and act autonomously, offering accurate predictions (Schubel et al., 2020). A collaboration between Laura® and researchers from the Federal University of Paraná (UFPR) resulted in Robot Laura®, which uses AI and ML to reduce sepsis deaths through early identification. This technology integrates data systems to collect information, perform statistical calculations, and provide conclusions about the presence of conditions favorable to sepsis. The study aimed to investigate the impact of these algorithms on healthcare professionals› decision-making and demonstrate how technology can contribute to nursing practice in sepsis patients (Schubel *et al.*, 2020).

Various ML algorithms are used for the diagnosis, prognosis, and phenotyping of sepsis. Supervised algorithms develop sepsis predictions, while unsupervised ones highlight underlying structures and hidden patterns. Supervised learning predominates in most diagnostic and prognostic applications, while unsupervised learning defines phenotypes, facilitating the use of specific therapies and the selection of patients for clinical trials (Komorowski *et al.*, 2022).

The COMPOSER model (COnformal Multidimensional Prediction Of SEpsis Risk) aims to predict the risk of sepsis early, minimizing false alarms (Komorowski et al., 2022). ML techniques reveal metabolic disturbances in sepsis, helping to distinguish between pathological conditions and predict different therapeutic responses (Komorowski *et al.*, 2022). Biomarkers and post-translational modifications (PTMs) during infections and immune responses are essential for the diagnosis and treatment of sepsis (Chang; Li, 2022).

In addition to technological advances, the discovery and evaluation of sepsis biomarkers have the potential to improve diagnostic accuracy, indicate physiological pathways, guide clinical trials, and optimize clinical management (Komorowski *et al.*, 2022). A wide variety of biomarkers have been identified, including PRMs, chemokines, cytokines, DAMPs, non-coding RNAs, microRNAs, cell membrane receptors, metabolites, cellular proteins, soluble receptors, and complement system components. The review focused on the application of the models (diagnostic, prognostic, or phenotyping) and the nature of the input data, whether routine (clinical and laboratory) or non-routine (gene expression, cytokines, metabolomics, among others) (Komorowski *et al.*, 2022).

Biomarkers such as procalcitonin, C-reactive protein, and inflammatory cytokines are used for sepsis diagnosis and prognosis (Huang; Cai and Su, 2019). Nanotechnology and biosensors also show promise for overcoming diagnostic challenges, offering greater sensitivity and specificity (Pant; Mackraj and Govender, 2021).

Transcriptomics aims to improve the precision of sepsis diagnosis by providing better information about infection severity and prognosis compared to current biomarkers. This approach offers a broader evaluation of the body›s response to infection through the analysis of the host immune gene expression profile (mRNA). The test known as SeptiCyte Lab is already being marketed (Immunexpress, Seattle, WA), and a version of the test that takes 4 to 6 hours has received FDA authorization to aid in differentiating sepsis positive from systemic infection negative in patients suspected of sepsis admitted to the ICU on the first day. In a study involving ICU patients, the SeptiCyte Lab showed significantly higher diagnostic accuracy in differentiating between sepsis and SIRS compared to PCT. Studies suggest that transcriptomics-based tests may outperform biomarkers. Another relevant aspect of transcriptomics study is distinguishing between bacterial and viral infections and its use in sepsis risk stratification (Gunsolus *et al.*, 2019).

Studies that analyzed the transcriptome identified several modules related to sepsis (GSE185263 and GSE65682), along with others such as M2, M33, M35, M57, and M63. For instance, M33 was upregulated in severe sepsis, septic shock, and sepsis death compared to SIRS. The study also reports that these modules can differentiate the infectious focus of bacterial pneumonia, influenza pneumonia, mixed bacterial and influenza pneumonia, and non-infectious SIRS (Li *et al.*, 2023).

Combining advanced techniques with different types of omics data, such as genomics, proteomics, transcriptomics, and metabolomics, has shown significant advances in sepsis research. Algorithms like Support Vector Machines (SVM), Random Forests, and Stabl have proven effective in discovering new biomarkers and immunological profiles, being crucial for early disease identification and the development of personalized therapeutic strategies. A good example is the NAVOY algorithm, which can predict sepsis in real-time, using four hours of collected laboratory values and clinical parameters to identify patients at risk of developing sepsis three hours before its onset (Santacroce *et al.*, 2024).

Advancements include the deacetylation of the p53 protein, which promotes autophagy in renal cells, and the identification of peptidylarginine deiminase 2 (PAD2) as a promising biomarker. Other important biomarkers are CitH3 and GPR174, which indicate sepsis severity and prognosis (Chang; Li, 2022). The discovery of biomarkers related to infection, inflammation, immune imbalance, and organ dysfunction is crucial for clinical diagnosis, monitoring, and therapeutic intervention. Biomarkers such as procalcitonin, C-reactive protein, and inflammatory cytokines play an important role in early diagnosis and prognosis of sepsis (Huang; Cai and Su, 2019).

The use of biological markers may never overcome the diagnostic and prognostic difficulties in sepsis due to the fact that the condition does not present a single clear pathophysiology but rather a varied set of severe inflammatory responses to infection. Therefore, a single elevated marker during a simple infection as well as in a critical non-infectious disease cannot reliably provide information about the presence of infection or

disease severity, requiring the association and analysis of various biomarkers (Gunsolus *et al.*, 2019).

Nanotechnology, with electrochemical, optical, magnetic sensors, and immunosensors, offers greater diagnostic sensitivity and specificity. Electrochemical biosensors and immunosensors allow the detection of various biomarkers with high precision (Pant; Mackraj and Govender, 2021). Systems biology approaches, such as transcriptomics, proteomics, and metabolomics, are expected to contribute to a better understanding of sepsis and the development of new biomarkers and diagnostic tools (Reinhart et al., 2012). The integration of advanced technologies and clinical information can improve diagnostic accuracy and timeliness, suggest therapeutic targets, and optimize clinical management (Komorowski *et al.*, 2022).

The evolution of diagnostic technologies and the use of ML offer new perspectives for the detection and treatment of sepsis. Collaboration between healthcare professionals and technology is fundamental to developing innovative solutions that improve patient outcomes (Komorowski *et al.*, 2022).

TREATMENT

Due to the high mortality rates associated with sepsis, it is essential to implement effective treatment and management strategies to ensure patient survival. Implementing promising therapeutic options that consider the severity of the condition can reduce mortality and increase patient survival. The need to offer personalized treatment presents a challenge due to the diverse clinical manifestations of the pathology. Therapeutic approaches include implementing an aggressive resuscitation plan, antimicrobial treatment, and, in some cases, steroid administration (Mirijello; Tosoni, 2020). The heterogeneous occurrence of the disease and its impact on various systems complicate the formulation of a uniform treatment plan (Purcarea; Sovaila, 2020).

Early detection of sepsis is crucial for increasing survival rates, and new diagnostic tools are being developed to diagnose the disease and enable immediate treatments (Mirijello; Tosoni, 2020). Transcriptome analysis and the identification of prognostic markers are essential for developing diagnostic biomarkers and empowering personalized therapy (Hunt, 2024). Extensive studies have revealed inflammatory imbalances, immune dysregulation, mitochondrial damage, and coagulation disorders. The development of the use of nanoparticles as adjuvants or antibiotic therapy has shown promising results in treating sepsis (Escartín; Martínez-López and Nadal-Barón, 2023). Omics technologies and artificial intelligence are revolutionizing the approach to sepsis, providing detailed profiles, identifying biomarkers, and selecting specific therapeutic agents (Tindal *et al.*, 2021).

Using these tools has the potential to improve clinical outcomes, considering the variability of sepsis among individuals and tailoring the therapeutic approach as needed.

Sympathetic treatment lines, studies with micronutrients, and antioxidant and anti-inflammatory therapies show promise, although further studies are necessary to confirm their efficacy and safety. Biomarkers such as leukocytosis, procalcitonin, CRP, lactate, interleukins, adrenomedullin, and presepsin have played crucial roles in diagnosing and monitoring sepsis treatment response, but no single biomarker is sufficiently reliable (Huang; Cai and Su, 2019). Combining data from different biomarkers can help make more accurate diagnoses and facilitate monitoring of the treatment response (Mirijello; Tosoni, 2021).

Current treatment options include aggressive resuscitation, antimicrobial medications, and eventually, steroid administration. However, the etiological diversity and the variety of systems affected during a septic response present significant difficulties for adequate treatment (Tindal *et al.*, 2021). Fluid administration is a cornerstone in managing hemodynamic instability, but optimizing this administration remains a challenge. Administering fluids in boluses can reduce arterial elastance, leading to vasodilation and a hyperdynamic state, while excessive administration is associated with organ dysfunction and death. To avoid delays in hemodynamic stabilization, early initiation of a vasopressor is recommended, although most vasopressors lack information on safe and effective doses. Antibiotic therapy is fundamental in treating sepsis, but inadequate therapy within the first 24 hours leads to eight times higher hospital mortality (Pant; Mackraj and Govender, 2021).

Moreover, some authors argue that the timing of interventions has an extreme impact on patient mortality. Thus, the 3-hour and 6-hour sepsis bundles should be replaced by a «1-hour bundle» with rapidly administered antibiotics and vasopressors. However, others believe this may lead to an undesirable increase in the use of antibiotics and vasopressors without solid evidence supporting this practice. The arbitrary «1-hour bundle» is not yet ready for real-world use, but early active resuscitation actions and protocolized follow-up are highly recommended. If there is no response to initial measures or if lactate levels remain elevated, immediate actions are necessary. Crystalloid solutions and antimicrobials are the foundation of therapy (Purcarea; Sovaila, 2020).

Despite the use of supportive therapy and adequate administration, antibiotics are often inefficient and have little effect on reducing the mortality rate from sepsis. Patients with sepsis-associated immune paralysis are susceptible to secondary infections, including invasive infections caused by multidrug-resistant (MDR) bacteria. Thus, these patients require specific strategies aimed at restoring immune function, in addition to antibiotic therapy and conventional treatments. These adjunctive therapies can help the immune system, prevent immune paralysis, and attenuate inflammatory responses (Pant; Mackraj and Govender, 2021).

Currently, new studies are focusing on improving biomarkers and gene expression for the early and specific detection of sepsis complications, promoting more adequate and individualized treatment. Another trend is the increasing inclusion of artificial intelligence resources for early detection and constant surveillance, aiming to improve identification

and action in the early stages. Nanotechnology has been prominent in combating infections caused by microorganisms, including those by resistant pathogens, revolutionizing the antimicrobial field. The use of nanotechnology-based biosensors represents a new strategy for the more sensitive diagnosis of sepsis-related biomarkers. These biomarkers are commonly evaluated for different purposes in the treatment of sepsis, such as diagnosis, prognosis, control, replacement, and stratification. Clinical detection of sepsis has been successful with the use of a small set of biomarkers, such as CRP, PCT, and interleukin-6 (IL-6) (Pant; Mackraj and Govender, 2021).

Biomarkers play a crucial role in the early detection of sepsis and risk classification, influencing therapeutic management, antibiotic administration, severity prediction, and evaluation of efficacy. Currently, more than 170 biomarkers have been discovered for the diagnosis of sepsis, highlighting PCT, CRP, IL-6, MCP-1, miRNA, among others (Huang, Cai & Su, 2019). CRP levels before treatment, obtained within a 48-hour interval, can be useful in assessing the response of patients with sepsis to antimicrobial therapy. Additionally, CRP at admission can be an important indicator of early infection and help in prognosis and treatment monitoring (Huang; Cai and Su, 2019). Elevated CRP levels can significantly correlate with infection severity, aiding in early diagnosis and prognosis in patients with sepsis (Pant; Mackraj and Govender, 2021). However, various non-infectious conditions can cause elevated CRP, resulting in low specificity for infections (Gunsolus *et al.*, 2019).

Procalcitonin (PCT) can be useful as a prognostic indicator in patients with sepsis. Although a single PCT value at the onset of the clinical condition is not very useful in predicting the patient›s outcome, several studies show that sequential measurement of PCT can help in assessing mortality risk. Additionally, it has been analyzed that the lack of a decrease or even an increase in its predictive value is associated with an unfavorable prognosis. Studies on patients with acute respiratory infections, including sepsis and septic shock, indicated that PCT-guided therapy resulted in lower antibiotic consumption, fewer side effects, and a lower fatality rate (Gunsolus *et al.*, 2019; Ehler; Busjahn and Schürholz, 2021).

Recent research has also revealed that microRNAs (miR-25) demonstrated higher diagnostic accuracy compared to previously mentioned markers, such as CRP and PCT. Moreover, the miRNA biomarker was able to distinguish between bacterial and viral causes of acute respiratory failure (Ehler; Busjahn and Schürholz, 2021).

Human studies have pointed to the relationship between persistent neutrophil dysfunction and increased risk of hospital infections, considering CD64 neutrophil (nCD64) a reliable marker to identify systemic infection, sepsis, and tissue injury with high sensitivity and specificity. According to research, patients exhibiting greater neutrophil dysfunction after sepsis are more likely to develop complications during ICU hospitalization. Despite producing low levels of cytokines, these neutrophils increase IL-10 production during sepsis, hindering T lymphocyte proliferation (Santacroce *et al.*, 2024). Evaluating interleukins, IL-6

is reduced in the first week of infection in survivors but increases in non-survivors. Thus, measuring IL-6 in neonatal sepsis diagnosis has proven to be an effective, non-invasive, and rapid method for early diagnosis (Huang; Cai and Su, 2019).

Analyzing presepsin (sCD14-ST) shows a significant increase within 2 hours of infection onset, peaking at 3 hours. Therefore, this biomarker currently holds potential for diagnosing adult sepsis, with several studies demonstrating that presepsin surpasses PCT, CRP, and IL-6 in terms of sensitivity and specificity in sepsis diagnosis. It can also effectively assess disease severity and prognosis (Huang; Cai and Su, 2019).

Currently, no specific and effective therapeutic drugs are available. The focus of drug development is on regulating inflammatory response, coagulation, and immune dysfunction, aiming to restore the body›s pro- and anti-inflammatory balance and improve patient prognosis. With advancements in sepsis treatment, there has been a significant reduction in the number of patients with multiple organ failure in the ICU. Persistent immune dysfunction is now the main cause of death in patients with advanced sepsis, making it the primary focus of medicinal treatment research. Some studies have evaluated immune responses in sepsis through the administration of TNF-α neutralizing antibodies, noting that two of these antibodies, Afelimomab and CytoFab, showed promise after some trials (Huang; Cai and Su, 2019).

Polymyxin B has antibacterial activity against Gram-negative bacteria and can bind and neutralize endotoxins that play a critical role in sepsis. A hemoperfusion system called polymyxin B (PMX-HP) was developed to remove endotoxins using polymyxin B as an adsorbent. Several studies have demonstrated the clinical efficacy of PMX-HP in patients with severe sepsis and septic shock, associating it with reduced mortality, improved hemodynamics, and increased pulmonary oxygenation in patients with septic shock (Huang; Cai and Su, 2019).

The administration of recombinant human soluble thrombomodulin (rhTM) for the treatment of disseminated intravascular coagulation (DIC) has been used in Japan for over a decade, showing promising results with a significant reduction in mortality (Huang; Cai and Su, 2019). Indeed, rhTM has proven effective in treating DIC, with phase III clinical studies demonstrating it to be more efficient than heparin in resolving the condition and ensuring patient safety. Some studies have shown that administering rhTM to septic patients significantly improved organ dysfunction according to Sequential Organ Failure Assessment (SOFA) scores and reduced mortality (Tindal *et al.*, 2021).

Regarding the immune dysfunction that occurs in septic patients, some studies have demonstrated that the use of PD-1, a negative costimulatory molecule, can reverse immunosuppression by decreasing apoptosis levels, stimulating the cytokine profile in an anti-inflammatory direction, and increasing the production of IFN-γ and IL-2. According to these studies, employing coinhibitory molecules can shift a hyper-inflammatory response to a hypoactive response, which is crucial to reducing the risk of secondary infections and mortality. Thus, this therapeutic approach emerges as one of the most promising in sepsis treatment in the coming years (Huang; Cai and Su, 2019; Tindal *et al.*, 2021).

The use of nanotechnology in antimicrobial treatment is being termed the «post-antibiotic era» due to the evolution of drug-resistant pathogens and the scarcity of new antibiotic research. Incorporating nanotechnology into antimicrobial drugs offers additional benefits beyond structural characteristics, such as overcoming resistance. For example, studies have shown that administering vancomycin through the CARG drug nanosystem was about ten times more effective than the free drug. Moreover, nanoparticle formulations can prolong the antibiotic›s lifespan, act as a gradual release system, reduce administration frequency, and improve therapeutic efficacy (Pant; Mackraj and Govender, 2021).

Transcriptome studies are also aiding in the analysis of candidate drugs for sepsis treatment. Some modules related to positive disease outcomes were enriched with phytoestrogen and ibuprofen genes. Other modules with negative outcomes were enriched with testosterone, urea, and vitamin B genes. These data can generate new hypotheses for potential medications as treatment options for sepsis (Li *et al.*, 2023).

Several studies have shown the benefits of using antioxidants, notably vitamin C, vitamin E, N-acetylcysteine, and melatonin, with results indicating that antioxidant therapy combined with standard therapy can reduce multiple organ failure, oxidative stress, and inflammation in patients with septic shock (Mirijello; Tosoni, 2021).

Melatonin is particularly interesting due to its protective effect, which includes inhibiting the activation of the NF-κB and NLRP3 inflammasome. The therapeutic approach using melatonin-loaded nanocarriers prevents its capture by macrophages, resulting in a prolonged circulation time. Additionally, this drug delivery system allows for on-demand delivery and targeted release at specific sites in response to the particular microenvironment rather than systemic administration of melatonin. This enables drug delivery to a specific location, relieving hepatic flow, which is often affected by sepsis (Pant; Mackraj and Govender, 2021).

Another recent research focus is the approach to gut microbiota, as the importance of the host flora in altering the immune response during sepsis has been emphasized, showing the predominance of certain bacterial communities after infection and apparently influencing the host›s reaction. Studies reveal that using prebiotics, probiotics, or symbiotics, and fecal transplantation could alter the microbiome, impacting clinical outcomes related to sepsis by acting as primary prevention, reducing the severity of the condition, and preventing secondary infections (Tindal *et al.*, 2021).

REFERENCES

CASSINI, Alessandro et al. Future directions and priorities in sepsis epidemiology research: a call for action. **Bulletin of the World Health Organization**, v. 99, n. 5, p. 398, 2021.

CHANG, Panpan; LI, Yongqing. Targeting Protein Post-Translational Modifications (PTMs) for Diagnosis and Treatment of Sepsis. **Frontiers in Immunology**, v. 13, p. 856146, 2022.

CHOU, Eric H. et al. Incidence, trends, and outcomes of infection sites among hospitalizations of sepsis: A nationwide study. **PloS one**, v. 15, n. 1, p. e0227752, 2020.

Ehler, J., Busjahn, C. & Schürholz, T. Which biomarkers are used to diagnose and control anti-infective therapy in sepsis?. **Anaesthesist** 71, 3–11 (2022).

ESCARTÍN, Maria Nieves Larrosa; MARTÍNEZ-LÓPEZ, Miguel Ángel; NADAL-BARÓN, Patricia. The microbiology of sepsis is more than the application of new technologies in diagnosis. **Revista Española de Quimioterapia**, v. 36, n. Suppl 1, p. 5, 2023.

FLEISCHMANN-STRUZEK, Carolin; RUDD, Kristina. Challenges of assessing the burden of sepsis. **Medizinische Klinik-Intensivmedizin und Notfallmedizin**, v. 118, n. Suppl 2, p. 68-74, 2023.

GUNSOLUS, Ian L. et al. Diagnosing and managing sepsis by probing the host response to infection: advances, opportunities, and challenges. **Journal of clinical microbiology**, v. 57, n. 7, p. 10.1128/jcm. 00425-19, 2019.

HUANG, Min; CAI, Shaoli; SU, Jingqian. The pathogenesis of sepsis and potential therapeutic targets. **International journal of molecular sciences**, v. 20, n. 21, p. 5376, 2019.

HUNT, Anne. Sepsis: an overview of the signs, symptoms, diagnosis, treatment and pathophysiology. **Emergency Nurse**, v. 32, n. 1, 2024.

KARAMPELA, Irene; FRAGKOU, Paraskevi C. Future perspectives in the diagnosis and treatment of sepsis and septic shock. **Medicina**, v. 58, n. 7, p. 844, 2022.

KOMOROWSKI, Matthieu et al. Sepsis biomarkers and diagnostic tools with a focus on machine learning. **EBioMedicine**, v. 86, 2022.

LÁSZLÓ, Ildikó et al. Sepsis: from pathophysiology to individualized patient care. **Journal of immunology research**, v. 2015, 2015.

LI, Qingsheng et al. A gene network database for the identification of key genes for diagnosis, prognosis, and treatment in sepsis. **Scientific Reports**, v. 13, n. 1, p. 21815, 2023.

LIPPI, Giuseppe. Sepsis biomarkers: past, present and future. **Clinical Chemistry and Laboratory Medicine (CCLM)**, v. 57, n. 9, p. 1281-1283, 2019.

MIRIJELLO, Antonio; TOSONI, Alberto. Sepsis: New Challenges and Future Perspectives for an Evolving Disease—Precision Medicine Is the Way!. **Medicina**, v. 57, n. 10, p. 1109, 2021.

MIRIJELLO, Antonio; TOSONI, Alberto; INTERNAL MEDICINE SEPSIS STUDY GROUP. New strategies for treatment of sepsis. **Medicina**, v. 56, n. 10, p. 527, 2020.

MOLNÁR, Zsolt et al. Sepsis: diagnostic and therapeutic challenges. **BioMed research international**, v. 2016, 2016.

PANDEY, Swarnima. Sepsis, Management & Advances in Metabolomics. **Nanotheranostics**, v. 8, n. 3, p. 270, 2024.

PANT, Amit; MACKRAJ, Irene; GOVENDER, Thirumala. Advances in sepsis diagnosis and management: a paradigm shift towards nanotechnology. **Journal of Biomedical Science**, v. 28, p. 1-30, 2021

PURCAREA, Adrian; SOVAILA, Silvia. Sepsis, a 2020 review for the internist. **Romanian Journal of Internal Medicine**, v. 58, n. 3, p. 129-137, 2020.

REINHART, Konrad et al. New approaches to sepsis: molecular diagnostics and biomarkers. **Clinical microbiology reviews**, v. 25, n. 4, p. 609-634, 2012.

SANTACROCE, Elena et al. Advances and Challenges in Sepsis Management: Modern Tools and Future Directions. **Cells**, v. 13, n. 5, p. 439, 2024.

SCHUBEL, Laura et al. Informatics and interaction: applying human factors principles to optimize the design of clinical decision support for sepsis. **Health informatics journal**, v. 26, n. 1, p. 642-651, 2020.

TIDSWELL, Robert; INADA-KIM, Matt; SINGER, Mervyn. Sepsis: the importance of an accurate final diagnosis. **The Lancet Respiratory Medicine**, v. 9, n. 1, p. 17-18, 2021.

TINDAL, Elizabeth W. et al. Emerging therapeutic targets for sepsis. **Expert opinion on therapeutic targets**, v. 25, n. 3, p. 175-189, 2021.

Chapter 8

SPONTANEOUS BACTERIAL PERITONITIS

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CHAPTER 8

SPONTANEOUS BACTERIAL PERITONITIS

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Spontaneous Bacterial Peritonitis (SBP) is a common complication in cirrhotic patients with ascites, characterized by an infection of the pre-existing peritoneal fluid without other intra-abdominal causes. Early diagnosis and treatment are crucial, as the lack thereof can result in fatal complications

(Milevoj Kopcinovic *et al.*, 2020). The mortality associated with SBP is approximately 20%, and recurrence rates remain high, even with therapeutic advances (Biggins *et al.*, 2021). Recent guidelines suggest that the global peritonitis episode rate should not exceed 0.40 per year and that more than 80% of patients should be free of peritonitis annually, emphasizing the importance of seeking evidence for strategies to reduce and prevent SBP (Li *et al.*, 2022).

The diagnosis of SBP requires a detailed investigation of ascites, including medical history, physical examination, and complementary tests (Li *et al.*, 2022). Imaging studies are valuable, especially in cases of small volumes of ascitic fluid, and diagnostic paracentesis is essential to identify the etiology (Milevoj Kopcinovic *et al.*, 2020). The polymorphonuclear (PMN) cell count in peritoneal fluid is the most reliable test to confirm SBP, with a count of 250 cells/mm³ or more being indicative of the disease (Sandhu; John, 2023). Empirical treatment should include third-generation cephalosporins, even in the absence of bacterial confirmation, and antibiotic prophylaxis is recommended for patients with cirrhosis, ascites, and hepatic or renal dysfunction (Sandhu; John, 2023). It is also important to consider evaluation for liver transplantation and the initiation of Renal Replacement Therapy (RRT) (Li *et al.*, 2022). In cases of persistent infection, such as Tertiary Peritonitis (TP), an integrated approach according to the Surviving Sepsis Campaign should be applied, including resuscitation, rapid source control, and empirical antibiotic therapy (Bass *et al.*, 2022).

Molecular techniques, such as PCR, have proven effective in rapidly detecting bacterial DNA in peritoneal fluid, and biomarkers can predict the development of SBP, improving diagnostic accuracy and enabling early interventions (Chaudhry *et al.*, 2019). Initial treatment with third-generation cephalosporins, such as cefotaxime, is recommended, with alternative options like ceftriaxone in case of resistance or allergy. Continuous prophylaxis with norfloxacin or ciprofloxacin is indicated for patients with low protein content in ascitic fluid or a history of SBP to reduce recurrence (Biggins *et al.*, 2021). The recent emphasis on multidisciplinary management and combined therapies aims to optimize clinical outcomes. Preventive strategies, such as the administration of prophylactic antibiotics before invasive procedures and strict hygiene practices in peritoneal dialysis, are essential to minimize infection risk (Chaudhry *et al.*, 2019).

EPIDEMIOLOGY

Demographic data indicate that peritonitis predominantly affects patients undergoing peritoneal dialysis (PD), with advanced age being a significant risk factor. There is no clear difference in incidence between genders; however, hygiene factors and underlying conditions may influence prevalence. Geographic incidence can vary depending on healthcare standards and peritoneal dialysis practices (Kotani *et al.*, 2021).

Historically, the incidence and prevalence of PD-related peritonitis have shown a downward trend, attributed to improvements in dialysis techniques, hygiene, and prophylactic antibiotic use. However, emerging antimicrobial resistance poses a significant challenge, impacting treatment efficacy and potentially increasing the associated mortality rate (Fiore *et al.*, 2019).

Statistics indicate that the mortality rate from peritonitis can be high, particularly in patients with severe underlying conditions. Studies show that survival rates can vary significantly depending on the speed and adequacy of the administered treatment. In some cases, mortality rates range from 20% to 40% in severe cases, especially when multidrug-resistant pathogens are involved (Kotani *et al.*, 2021).

The risk factors associated with peritonitis include age over 50 years (Gueiros *et al.*, 2022). When age is 65 years or older, in elderly patients, there is a higher likelihood of developing generalized peritonitis. This is due to factors such as late presentation to health services, altered clinical manifestations, and diminished local peritoneal responses. Generalized peritonitis has a high mortality rate, and its risk factors are multifaceted. For example, in sub-Saharan Africa, specific etiologies such as perforation caused by typhoid fever, postoperative peritonitis, and peptic ulcer perforation have been identified as major contributors to high mortality rates (Tochie *et al.*, 2020). Additionally, organ dysfunction and the presence of malignancy are significantly associated with mortality, which increases proportionally with age (Gueiros *et al.*, 2022).

In patients undergoing peritoneal dialysis, C-reactive protein (CRP) is a laboratory marker that acts as a risk factor. Elevated CRP levels indicate an immune inflammatory response, while elevated alkaline phosphatase (ALP) reflects a higher risk of short-term adverse outcomes and is associated with technical failures. High levels of low-density lipoprotein (LDL) are also associated with an increased risk of technical failures, as is the presence of fungi, which represent an additional risk in peritoneal dialysis (Yu *et al.*, 2023).

Although Serratia, a gram-negative organism, is a rare cause of peritonitis, it is a notable risk factor, with studies indicating that it accounts for approximately 1% of total cases (Au *et al.*, 2021). Peritonitis caused by Streptococcus oralis, although rare, presents a risk of recurrence months after the first episode and can result in long-term refractory peritonitis, with up to 41% of cases attributed to viridans group streptococci (Kotani *et al.*., 2021).

Risk factors for peritonitis after gastroscopy in peritoneal dialysis patients mainly include the use of gastric acid suppressants, which are associated with higher rates of adverse events and an increased risk of enteritis. Other relevant factors include the post-procedural microbiological profile, the timing of peritonitis onset, and the potential impact of prophylactic antibiotics (Chan *et al.*, 2022).

In patients with end-stage liver disease, risk factors for spontaneous bacterial peritonitis include increased bacterial resistance, the growing use of quinolones for

prophylaxis, and the severity of cases. Inadequate antibiotic therapy contributes to morbidity and mortality in patients with SBP (Fiore *et al.*, 2019).

DIAGNOSIS

The prevalence of SBP varies from 3.5% to 30% depending on the clinical setting, and early diagnosis is crucial to reducing mortality, which has decreased from 90% to about 20% with more rapid interventions. Each hour of diagnostic delay is associated with a 3.3% increase in hospital mortality risk (Luo *et al.*, 2019; Popoiag; Fierbințeanu-Braticevici, 2021). Late diagnosis can result in treatment delays, generating high hospital costs and compromising patients' quality of life due to additional complications (Buckup *et al.*, 2022).

The gold standard for diagnosing peritonitis is the polymorphonuclear cell count in ascitic fluid, with values above 250 cells/mm³, a process that can be time-consuming (Patel *et al.,* 2022). The diagnosis of refractory ascites is also important, as it increases the risk of peritonitis, with relevant criteria including early recurrence, diuretic resistance, or intolerance (Khan; Linganna, 2023). Patients with recent ascites, increased abdominal distension, and signs indicating SBP should undergo diagnostic paracentesis (Khan; Linganna, 2023).

CLINICAL MANIFESTATIONS

Patients with SBP may present a wide range of symptoms or even be asymptomatic, especially in the early stages of the disease, making early diagnosis challenging (Luo *et al.*, 2019; Popoiag; Fierbințeanu-Braticevici, 2021). The symptoms most frequently associated with SBP include abdominal pain and tenderness on palpation, with a diagnostic sensitivity of 94%. Other clinical manifestations may include vomiting, diarrhea, hyper or hypothermia, chills, tachycardia, tachypnea, jaundice, and leukocyte changes. Complications associated with SBP may involve liver failure, mental state alterations due to hepatic encephalopathy, hepatorenal syndrome, coagulopathies, and gastrointestinal bleeding (Luo *et al.*, 2019; Popoiag; Fierbințeanu-Braticevici, 2021).

However, the diagnosis of SBP cannot be based solely on clinical signs. Although a history of fever in the past 24 hours has a specificity of 81%, it cannot differentiate SBP from other sources of infection. Clinical judgment, in turn, has shown limited sensitivity of 77% and specificity of 34% for detecting SBP, indicating that it is not sufficient for a definitive diagnosis. Therefore, it is necessary to perform a paracentesis to collect and analyze ascitic fluid (Popoiag; Fierbințeanu-Braticevici, 2021).

One of the complications of SBP is acute kidney injury, defined as an increase in creatinine greater than 0.3 mg/dL in 48 hours or a 50% increase in creatinine in 7 days. Hepatorenal syndrome is diagnosed after excluding hypovolemia/shock, exposure to nephrotoxic agents, and structural kidney damage in a patient with ascites (Khan; Linganna, 2023).

DIAGNOSTIC METHODS

Paracentesis is an essential procedure, not only to relieve ascites symptoms but also to diagnose potentially serious conditions. This method confirms the presence of infection and identifies the underlying cause of peritonitis, guiding appropriate treatment. Studies indicate that patients with SBP who undergo paracentesis within the first 12 hours of hospitalization have a mortality rate of 5.5%, compared to 7.5% for those who undergo the procedure later (Popoiag; Fierbințeanu-Braticevici, 2021).

Diagnostic paracentesis is recommended primarily in patients who present one of the following conditions: grade 2 or 3 ascites, hospitalization for worsening ascites, or complications arising from liver cirrhosis (Popoiag; Fierbințeanu-Braticevici, 2021). The gold standard for diagnosing peritonitis is the polymorphonuclear neutrophil (PMN) count in the collected fluid, with a value greater than 250 cells/mm³ confirming the disease in patients with SBP (Luo *et al.*, 2019). Flow cytometry is an innovative alternative, with a sensitivity and specificity of about 100% for detecting PMN at levels above 250 cells/mm³. Ascitic fluid culture is essential to guide antibiotic treatment, although it is not decisive for confirming the diagnosis (Popoiag; Fierbințeanu-Braticevici, 2021).

Blood culture analysis is important for diagnostic confirmation since the PMN count in ascitic fluid can be operator-dependent (Luo *et al.*, 2019). There are reports in the literature of cases where ascitic fluid analysis did not reveal the presence of bacteria despite the presence of polymorphonuclear leukocytes and a clinical picture suggestive of peritonitis. Thus, blood culture also plays a fundamental role in guiding treatment and defining the etiological diagnosis (Hadano, 2024).

RECENT ADVANCES IN DIAGNOSIS

Among biomarkers, procalcitonin (PCT) and high-sensitivity C-reactive protein (hs-CRP) have shown potential, although the association of PCT with SBP is still debated. Lactoferrin and calprotectin have demonstrated high sensitivity and specificity in diagnosing SBP but require further studies (Popoiag; Fierbințeanu-Braticevici, 2021). Additionally, prostaglandin E2 (PGE2) may be a promising biomarker for predicting hospital mortality in decompensated cirrhosis (Luo *et al.*, 2019).

Technologies like OpticLine, which use microscopy to detect infections early, and leukocyte esterase reagent strips (LERS) are being evaluated as useful diagnostic tools, despite variability in results (Patel *et al.*, 2022).

Recently, studies have suggested that low levels of potassium, albumin, and vitamin B12 may be associated with the risk of fungal peritonitis, with hypokalemia and oxidative stress potentially contributing to the condition's development. Hypoproteinemia and vitamin B12 deficiency are also linked to this pathology, highlighting the need for more reliable biomarkers for diagnosis (Liu *et al.*, 2021).

TREATMENT

Bacterial peritonitis is an infection with a high mortality rate if not treated promptly, with its mortality associated with systemic inflammation and sepsis. Appropriate and timely antibiotic therapy is crucial for all forms of bacterial peritonitis, and the antibiotic strategy can vary considerably due to microbiological diversity. Patients with spontaneous bacterial peritonitis should receive intravenous broad-spectrum antibiotics along with albumin, while those on peritoneal dialysis should receive intraperitoneal treatment. Secondary peritonitis, on the other hand, usually requires surgical intervention or interventional procedures (Pörner *et al.*, 2021).

Guidelines emphasize the importance of infection severity and local resistance profile in the initial treatment of SBP. Treatment should be initiated immediately after diagnosis to minimize complications and improve survival, with a diagnostic paracentesis performed 48 hours after treatment initiation to assess its effectiveness; a 25% reduction in leukocyte count indicates a good response (Popoiag; Fierbințeanu-Braticevici, 2021). Broad-spectrum treatments are recommended for critically ill patients, with variations in coverage for community-acquired and healthcare-related infections, with coverage for enterococci and multidrug-resistant bacteria indicated in specific situations such as septic shock (Montravers *et al.*, 2016).

The usual treatment for peritonitis in patients undergoing automated peritoneal dialysis (APD) involves the administration of antibiotics via the intraperitoneal (IP) route, preferably once a day, following recommendations based on continuous ambulatory peritoneal dialysis (CAPD) regimens. First-generation cephalosporins, such as cefazolin, are frequently used, with dosages adjusted according to pharmacokinetics. Studies suggest that continuous dosing may be more effective than intermittent dosing (Mancini; Piraino, 2019).

Empirical treatment for secondary peritonitis includes combining second- or third-generation cephalosporins with metronidazole or piperacillin/sulbactam. In more severe cases, carbapenems such as meropenem are used due to their broad antibacterial coverage. The combination of meropenem and vancomycin has demonstrated high efficacy, with a sensitivity rate of 98% for various bacteria. Treatment should be adjusted based on the patient's clinical response (Grotelüschen *et al.*, 2020).

Surgical treatment options depend on the severity of peritonitis and findings during the procedure. Minimally invasive procedures are preferred when feasible, but severe cases may require open surgery. Perioperative care, including analgesia, sedation, hemodynamic and ventilatory monitoring, and nutritional support, is crucial for effective peritonitis management (Montravers *et al.*, 2016).

Antibiotic treatment for SBP has evolved over time. Although serum levels have shown no significant difference between patients with and without dialysis-associated peritonitis

(DAP), ascitic fluid levels were significantly higher, with a cut-off value of 69.4 pg/mL showing a sensitivity of 80% and specificity of 72.7%, and an area under the curve (AUROC) of 0.77 for the diagnosis of DAP. The 2010 EASL guideline recommends cefotaxime (2 g every 12 or 8 hours for 5 days) as the first-line treatment. Alternatives include amoxicillin/clavulanic acid and quinolones such as ciprofloxacin and ofloxacin (Popoiag; Fierbințeanu-Braticevici, 2021).

Additionally, the administration of albumin has been shown to reduce mortality and the incidence of acute kidney injury (AKI) in patients with SBP. Albumin administration in DAP is recommended within 6 hours of diagnosis, especially in high-risk patients with the following laboratory results: serum creatinine > 1 mg/dL, blood urea nitrogen > 30 mg/dL, or total bilirubin > 4 mg/dL (Ebied *et al.*, 2022).

Peritonitis resulting from enteric conditions such as strangulated intestine, ischemic colitis, and appendicitis can be difficult to diagnose, leading to delays in appropriate treatment and consequently increased morbidity, with a mortality rate of around 50%. Additionally, peritonitis caused by coagulase-negative staphylococci presents an additional challenge due to the high proportion of methicillin-resistant strains and their ability to form biofilms. The methicillin resistance rate among these staphylococci, responsible for peritonitis, has increased to over 50% in most centers, potentially reaching up to 70%. This requires personalized approaches and strict monitoring to improve clinical outcomes and reduce the morbidity and mortality associated with the condition (Li *et al.*, 2022).

REFERENCES

AU, Christy WH, *et al.* Exit site infection and peritonitis due to Serratia species in patients receiving peritoneal dialysis: epidemiology and clinical outcomes. **Nephrology**, v. 26, n. 3, p. 255-261, 2021.

BASS, Gary Alan, *et al.* Tertiary peritonitis: considerations for complex team-based care. **European Journal of Trauma and Emergency Surgery**, v. 48, n. 2, p. 811-825, 2022.

BIGGINS, Scott W., *et al.* Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. **Hepatology**, v. 74, n. 2, p. 1014-1048, 2021.

BUCKUP, Mark, *et al.* Utilising low-cost, easy-to-use microscopy techniques for early peritonitis infection screening in peritoneal dialysis patients. **Scientific Reports**, v. 12, n. 1, p. 14046, 2022.

CHAN, Gordon Chun-Kau, *et al.* Risk of peritonitis after gastroscopy in peritoneal dialysis patients. **Peritoneal Dialysis International**, v. 42, n. 2, p. 162-170, 2022.

CHAUDHRY, Rafia I., *et al.* Strategies to prevent peritonitis after procedures: our opinions. **Peritoneal Dialysis International**, v. 39, n. 4, p. 315-319, 2019.

EBIED, Alex M., *et al.* Albumin utilization in spontaneous bacterial peritonitis. **Journal of pharmacy practice**, v. 35, n. 4, p. 546-550, 2022.

FIORE, Marco, *et al*. Spontaneous bacterial peritonitis caused by Gram-negative bacteria: an update of epidemiology and antimicrobial treatments. **Expert Review of Gastroenterology & Hepatology,** v. 13, n. 7, p. 683-692, 2019.

GROTELÜSCHEN, Rainer, *et al.* Antibiotic sensitivity in correlation to the origin of secondary peritonitis: a single center analysis. **Scientific Reports**, v. 10, n. 1, p. 18588, 2020.

GUEIROS, Laís Dos Santos, *et al.* Mannheim's peritonitis index in the prediction of postoperative outcome of peritonitis. **Revista do Colégio Brasileiro de Cirurgiões**, v. 49, p. e20222991, 2022.

HADANO, Yoshiro. Use of Blood Culture Bottles in the Diagnosis of Spontaneous Bacterial Peritonitis. **Internal Medicine**, v. 63, n. 3, p. 465-465, 2024.

KHAN, Sarah; LINGANNA, Maureen. Diagnosis and management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome. **Cleveland Clinic journal of medicine**, v. 90, n. 4, p. 209-213, 2023.

KOTANI, Akihiro, *et al*. Peritoneal dialysis-related peritonitis caused by Streptococcus oralis. **Internal Medicine**, v. 60, n. 21, p. 3447-3452, 2021.

LI, Philip Kam-Tao, *et al.* ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment. **Peritoneal dialysis international**, v. 42, n. 2, p. 110-153, 2022.

LIU, Lingling, *et al*. Serum potassium, albumin and vitamin B12 as potential oxidative stress markers of fungal peritonitis. **Annals of Medicine**, v. 53, n. 1, p. 2132-2141, 2021.

LUO, Junli, *et al*. Role of ascitic prostaglandin E2 in diagnosis of spontaneous bacterial peritonitis and prediction of in-hospital mortality in patients with decompensated cirrhosis. **Medicine**, v. 98, n. 26, p. e16016, 2019.

MANCINI, Ann; PIRAINO, Beth. Review of antibiotic dosing with peritonitis in APD. **Peritoneal Dialysis International**, v. 39, n. 4, p. 299-305, 2019.

MILEVOJ KOPCINOVIC, Lara, *et al.* Laboratory testing of extravascular body fluids: National recommendations on behalf of the Croatian Society of Medical Biochemistry and Laboratory Medicine. **Part I–Serous fluids. Biochemia medica,** v. 30, n. 1, p. 31-59, 2020.

MONTRAVERS, P., *et al*. Therapeutic management of peritonitis: a comprehensive guide for intensivists. **Intensive care medicine**, v. 42, p. 1234-1247, 2016.

PATEL, Kishan P., *et al.* Performance of leukocyte esterase reagent strips in the detection of spontaneous bacterial peritonitis in cirrhotic patients: A systematic review and meta-analysis. **Journal of Clinical and Experimental Hepatology**, v. 12, n. 2, p. 519-532, 2022.

POPOIAG, Roxana-Emanuela; FIERBINȚEANU-BRATICEVICI, Carmen. Spontaneous bacterial peritonitis: update on diagnosis and treatment. **Romanian Journal of Internal Medicine**, v. 59, n. 4, p. 345-350, 2021.

PÖRNER, Daniel, *et al*. Advances in the pharmacological management of bacterial peritonitis. **Expert Opinion on Pharmacotherapy**, v. 22, n. 12, p. 1567-1578, 2021.

SANDHU, Sunny; JOHN, Binu V. Spontaneous Bacterial Peritonitis: The Bug Matters. **Digestive Diseases and Sciences,** v. 68, n. 5, p. 1667-1669, 2023.

TOCHIE, Joel Noutakdie, *et al.* Global epidemiology of acute generalised peritonitis: a protocol for a systematic review and meta-analysis. **BMJ open**, v. 10, n. 1, p. e034326, 2020.

WATTERS, James M., *et al.* The influence of age on the severity of peritonitis. **Canadian journal of surgery**, v. 39, n. 2, p. 142, 1996.

YU, Jin, *et al*. Technique failure in peritoneal dialysis-related peritonitis: risk factors and patient survival. **Renal Failure**, v. 45, n. 1, p. 2205536, 2023.

Chapter 9

ACUTE APPENDICITIS

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CHAPTER 9

ACUTE APPENDICITIS

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The cecal appendix is a closed-ended tube located in the cecal region. Acute appendicitis is characterized by luminal obstruction of the appendix, often caused by mucosal inflammation, lymphoid hyperplasia, or fecalith. This condition is considered one of the most common surgical emergencies worldwide, affecting both adults and children. The luminal obstruction promotes bacterial proliferation,

leading to organ distension, increased intraluminal pressure, and potentially progressing to suppurative transmural inflammation, infarction, and perforation. The inflamed appendix can be isolated by the omentum and surrounding viscera, forming an inflammatory mass. Conversely, perforation can result in generalized peritonitis or an isolated appendicular abscess (Gutierrez *et al.*, 2022; Jumah; Wester, 2022; Juremeira *et al.*, 2022; Stringer, 2017).

It is estimated that about 8% of the world's population undergoes surgical procedures to treat this condition throughout their lives, and approximately 30% of children with acute abdominal pain referred to pediatric surgical services have acute appendicitis. Diagnostic methods will be analyzed, emphasizing traditional and advanced techniques for accurate and early detection, as well as common signs and symptoms associated with the condition. Finally, the importance of effective treatment will be discussed, including the timing and modalities of surgical interventions, as well as new tools for managing appendicitis (Jumah; Wester, 2022; Stringer, 2017).

Technical and instrumental advancements have consolidated laparoscopic appendectomy as the current standard treatment. Studies show that in adults, this approach results in a statistically significant reduction in wound infection incidence, hospital stay length, and postoperative complications, as well as a quicker return to work; however, these conclusions do not apply to the pediatric population (Wagner; Tubre; Asensio, 2018). Additionally, non-operative treatment of uncomplicated acute appendicitis, including antibiotic therapy, has been proposed as an effective and safe primary option, with a lower complication profile and reduced cost, promising to avoid unnecessary surgeries in both adults and children (Jumah; Wester, 2022).

EPIDEMIOLOGY

Acute appendicitis is one of the most common causes of abdominal pain, affecting about 10% of the population, with a peak incidence in the second or third decade of life, especially during the summer. In developed countries, the rate is 100 cases per 100,000 inhabitants per year, resulting in more than 300,000 appendectomies annually in the United States, of which less than 10% involve healthy appendices (Juremeira *et al.*, 2022; Snyder; Guthrie and Cagle, 2018). The prevalence is higher in young adults, particularly in men, with a lifetime risk of 8.6% for them and 6.7% for women. Despite this, appendectomies are performed twice as often in women, even with lower prevalence (Snyder; Guthrie and Cagle, 2018). Although the incidence of appendicitis decreases with age, the risk of perforation and neoplasia increases (Perez; Allen, 2018).

Perforation is the most concerning complication of appendicitis, potentially causing abscesses, peritonitis, bowel obstruction, fertility issues, and sepsis. The perforation rate in adults ranges from 17% to 32%. In children, a delay of more than 48 hours from symptom onset to diagnosis and surgery increases the perforation rate and hospital stay length

(Snyder; Guthrie; Cagle, 2018).

Appendicitis is the most common non-obstetric surgical emergency during pregnancy, with an incidence of 6.3 per 10,000 pregnancies in the pre-partum period, increasing to 9.9 per 10,000 after delivery. In the United States, more than 300,000 appendectomies are performed annually, with less than 10% resulting in the removal of a normal appendix (Snyder; Guthrie and Cagle, 2018).

Appendix neoplasia is more common in patients with complicated appendicitis. In cases treated with interval appendectomy, the rate of mucinous neoplasia reaches 55%. Interval appendectomy is an alternative strategy, especially recommended for patients over 40 years old, aiming to reduce the risk of appendix neoplasia, which can occur in up to 12% of cases treated this way (Perez; Allen, 2018).

Between 1973 and 2004, 2,791 patients with malignant appendix neoplasms were studied. Adenocarcinomas were the most frequent, accounting for 65.4% of cases. During this same period, there was a 260% increase in appendix carcinoma rates. The 5-year survival rate for these patients was 46.5%. For mucinous cystadenocarcinoma, the 5-year survival rate was 59% across all stages, while for signet ring cell tumors, it was 20.3%. Goblet cell carcinoid tumors, which represent less than 5% of primary appendix tumors and are composed of a mix of goblet and neuroendocrine cells, have a 5-year survival rate ranging from 40% to 75%, which is lower than that of well-differentiated NETs (Teixeira *et al.*, 2017).

The incidence of appendicitis in the elderly shows a lower preoperative diagnosis rate, with an accuracy of 64% compared to 78% in younger age groups. Mortality in the elderly reaches 8%, while in younger patients it ranges from 0% to 1%. Furthermore, the rate of complicated appendicitis, with perforation or abscess, is higher in the elderly, varying from 18% to 70%, compared to 3% to 29% in younger patients. Postoperative complication rates are also higher in elderly patients, with increased postoperative mortality and morbidity (Fugazzola *et al.,* 2020).

DIAGNOSIS

Early diagnosis of acute appendicitis must be performed accurately and efficiently to reduce morbidity and mortality and minimize the risk of complications such as perforation, generalized peritonitis, and sepsis (Snyder; Guthrie and Cagle, 2018). Acute appendicitis is considered a challenge for the healthcare system due to its high global prevalence. Thus, early diagnosis is crucial to reduce the chances of complications and the high costs associated with hospitalizations (Juremeira *et al.*, 2022).

History taking and physical examination, along with laboratory findings, remain the basis for avoiding late diagnosis (Bom *et al.*, 2021). Clinically, periumbilical abdominal pain that intensifies over 24 hours and migrates to the right iliac fossa is common in

more than half of patients with acute appendicitis. Other symptoms include colic, nausea, vomiting, anorexia, and fever. Changes in bowel habits, such as constipation and diarrhea, are frequent, as well as urinary changes when the appendix is located near the bladder (Juremeira *et al.*, 2022).

The pain caused by localized peritonitis can worsen with movements such as coughing or driving on bumpy roads (Baird *et al.*, 2017). Fever and anorexia arise as the infection evolves from a localized inflammatory process to a systemic inflammatory process. The disease can progress to perforation and peritonitis within 2 to 3 days after symptom onset. If the perforation occurs in an area of the abdomen confined by other intestinal loops, mesentery, or omentum, the infection remains localized in the lower right quadrant, resulting in continuous pain in that region without signs and symptoms of peritonitis. Occasionally, a mass may be palpated (Wagner; Tubre and Asensio, 2018).

There are three well-described anatomical positions for the appendix: ascending appendix, iliac appendix, and pelvic appendix. When the appendix is located in the retrocecal position, local symptoms tend to be mild or even absent. Pelvic appendices can cause pain in the suprapubic region, urinary symptoms, or pain when defecating if they are close to the rectum (Wagner; Tubre and Asensio, 2018). The variable position of the appendix results in different clinical manifestations, making diagnosis challenging, especially in pregnant women and women with gynecological complaints such as pelvic inflammatory disease. In children, however, the absence or reduction of bowel sounds, psoas sign, obturator sign, and Rovsing's sign are more reliable for diagnosing acute appendicitis.

In adults, the main signs and symptoms of acute appendicitis include pain in the lower right quadrant, abdominal rigidity, and pain radiating from the periumbilical region to the iliac fossa. In the elderly, clinical characteristics may be more silent, often due to the formation of an appendicular abscess or obstruction by perforation (Snyder; Guthrie and Cagle, 2018; Juremeira *et al.*, 2022). Specific physical examination findings for acute appendicitis include psoas sign, obturator sign, and Rovsing's sign (Snyder; Guthrie; Cagle, 2018). Abdominal examination usually reveals tenderness at McBurney's point, near the right iliac fossa (Wagner; Tubre and Asensio, 2018).

Blumberg's sign or rebound tenderness is provoked by gentle percussion or the rapid release of pressure at McBurney's point, indicating inflammatory irritation of the parietal peritoneum. Rovsing's sign involves palpation of the left iliac fossa that causes pain in the right iliac fossa. Psoas sign is positive when the appendix is located near the psoas or internal obturator muscles, inducing contraction of these muscles by flexing the hip or external rotation, respectively, causing intense pain. Obturator sign involves pain during passive internal rotation of the flexed thigh. Dunphy's sign is a useful technique in children, which includes making them jump, cough, or shake the bed. Rectal examination can provoke pain when palpating an inflamed pelvic appendix near the rectum (Wagner; Tubre and Asensio, 2018).

Laboratory tests alone have low sensitivity and specificity, but combined with patient

clinical data, they increase diagnostic accuracy, helping to exclude other pathologies and support the diagnosis of acute appendicitis (Hoffmann; Anthuber, 2019). The suspicion of appendicitis increases when there is an elevation in the white blood cell count, C-reactive protein concentration, granulocyte count, or the proportion of polymorphonuclear cells (Baird *et al.*, 2017). Other markers such as interleukins, procalcitonin, calprotectin, bilirubin, fibrinogen, and the APPY1 test have been studied. In cases of perforation, bilirubin should be considered, as studies show a specificity of 86% and sensitivity of 70%, compared to serum bilirubin levels in patients without perforation (Perez; Allen, 2018).

Urine examination can also help determine if the complaints and clinical findings are of urological origin. In women of childbearing age, it is important to rule out pregnancy as the cause of symptoms and consider alternative diagnoses such as renal colic or urinary tract infection. Due to the proximity of the appendix to the urinary tract, about 40% of patients with acute appendicitis may present leukocytes in the urine (Wagner; Tubre and Asensio, 2018).

Although the diagnosis of acute appendicitis is based on clinical history and physical examination, imaging exams such as ultrasound, abdominal computed tomography (CT), and magnetic resonance imaging (MRI) are frequently used (Perez; Allen, 2018). The more advanced the inflammatory process, the more evident the appendicitis will be in any of the imaging modalities. Each method has its advantages and disadvantages in terms of sensitivity, specificity, costs, and exposure to ionizing radiation (Baird *et al.*, 2017).

Computed tomography is highly sensitive (97-100%) and has a specificity of 90%, being considered the best diagnostic option despite its limitations in terms of cost, availability, and radiation exposure (Juremeira *et al.*, 2022; Wagner, Tubre and Asensio, 2018). It is contraindicated in pregnancy and relatively contraindicated in young people due to the increased risk of neoplasms. CT is useful for identifying inflammation, precise location, and excluding differential diagnoses, although it is unreliable for determining appendicular perforation (Hoffmann; Anthuber, 2019; Baird *et al.,* 2017). CT can define the diameter of the appendix, indicating appendicitis if greater than 6 mm, as well as the presence of fecaliths and/or periappendicular inflammation (Perez; Allen, 2018). Studies indicate that low-dose contrast-enhanced CT has comparable accuracy to normal CT and should be preferred. CT protocols generally use helical scanners with a slice thickness of 3 to 5 mm and an interval of 3 to 10 mm (Bom *et al.*, 2021).

Ultrasonography has a sensitivity of 80-94% and a specificity of 89-95%, being a non-invasive and economical option, but less accurate in obese patients and dependent on the operator's skill. It is safe for use in children and pregnant women (Juremeira *et al.*, 2022; Wagner; Tubre and Asensio, 2018). In sexually active women, transvaginal ultrasonography can be useful for visualizing gynecological organs. The accuracy of results depends on the operator's skill, with a specialist, such as a consultant radiologist, more likely to provide an accurate diagnosis (Baird *et al.*, 2017). In USG, it is important to mention whether the appendix is fully visualized, its diameter, and the state of its wall, as well as indirect signs of appendicitis such as free fluid, fat stranding, and small bowel dilation in the lower right

abdomen.

The diagnostic accuracy of magnetic resonance imaging is comparable to computed tomography and superior to ultrasonography, with a sensitivity of approximately 97% and specificity of about 97%, without the use of ionizing radiation. However, its cost is generally higher compared to CT and the procedure time is longer, making it not the first choice (Wagner; Tubre; Asensio, 2018; Perez; Allen, 2018). MRI or ultrasound techniques are more commonly used in pregnant women and children to avoid excessive radiation exposure (Hoffmann; Anthuber, 2019).

The Alvarado score, pediatric appendicitis score, and appendicitis inflammatory response score use clinical and laboratory findings to classify patients into low, moderate, or high risk, helping to make a more accurate diagnosis, as illustrated in Table 1 (Snyder; Guthrie and Cagle, 2018).

Table 1: Alvarado Score for Diagnosis of Acute Appendicitis

Clinical Criterion	
Symptoms	**Score**
Migratory pain to the right iliac fossa	1
Anorexia	1
Nausea or vomiting	1
Signs	
Pain on palpation in the right iliac fossa	2
Rebound (Blumberg)	1
Fever (>37.5°C)	1
Laboratory Findings	
Leukocytosis (>10,000/mm³)	2
Left shift of neutrophils	1
Total	10

Source: Snyder; Guthrie; Cagle, 2018.

Interpretation of the Score:

- 1-4: Low probability
- 5-6: Moderate probability
- 7-10: High probability

TREATMENT

Open appendectomy was described by Charlie McBurney in 1891, and the technique has remained largely unchanged (Téoule *et al.*, 2020). Regarding the choice

between conventional and laparoscopic surgery, numerous comparative studies have been conducted. For example, a meta-analysis of 33 prospective randomized controlled trials involving over 3,500 patients demonstrated that laparoscopic appendectomy in adults resulted in a statistically significant reduction in wound infection incidence, hospital stay length, and postoperative complications, as well as an earlier return to work, although with a longer operation time. However, this conclusion did not apply to the pediatric population (Wagner; Tubre and Asensio, 2018).

The Children's Interval Appendectomy (CHINA) study, a randomized multicenter clinical trial, addressed this issue in pediatric patients. Patients were randomized into two groups: one received antibiotic treatment and the other underwent appendectomy 66 days after treatment allocation. Appendectomy was associated with low complications and a high recovery rate; however, 6% of patients had severe complications and one patient required multiple surgeries (Jumah; Wester, 2022). Current evidence is insufficient to detect any significant advantage of antibiotic treatment compared to surgical treatment. Thus, surgery remains the treatment of choice for uncomplicated acute appendicitis in children (Teixeira *et al*, 2017).

Intravenous resuscitation is generally performed with normal saline solution, considering the patient's fluid deficit based on clinical signs of dehydration and tissue perfusion. In patients with generalized peritonitis, plasma electrolytes should be checked and fluids and electrolytes adjusted accordingly (Teixeira *et al*, 2017). Antibiotics are administered to prevent intra-abdominal abscess formation, wound infection, and sepsis. Antibiotic therapy, with cefuroxime plus metronidazole or amoxicillin/clavulanic acid, is initiated immediately after the diagnosis of acute appendicitis and always before surgery (Stringer, 2017).

Isolated antibiotic therapy, covering Gram-negative and anaerobic bacteria, has been increasingly used due to its potential to significantly reduce the costs associated with surgery (Iamarino *et al*, 2017). Given the risks associated with open and laparoscopic appendectomy, antibiotic therapy should be considered an effective option for adults and children. Patient management should always be performed in consultation with the surgical team, according to local hospital protocols and in a shared decision-making process (Snyder; Guthrie and Cagle, 2018).

Emerging evidence indicates that antibiotic therapy can be a first-line option for selected patients with uncomplicated appendicitis. A meta-analysis of five randomized clinical trials compared antibiotic treatments with appendectomy in 980 adults with uncomplicated appendicitis, demonstrating that antibiotic treatment resulted in a reduction in complication rates, fewer medical leaves or disability, and less need for analgesics. However, 40% of patients treated with antibiotics required appendectomy within the following year, compared to 8.5% of those who initially had surgery and needed a second intervention (Snyder; Guthrie and Cagle, 2018).

More recently, a randomized, multicenter, open-label clinical trial with 530 adults

aged 18 to 60 years with uncomplicated appendicitis reported a resolution rate of 73% with ertapenem (Invanz), 1 g per day intravenously for three days, followed by levofloxacin (Levaquin) for seven days, 500 mg per day, plus metronidazole (Flagyl), 500 mg three times a day (Snyder; Guthrie and Cagle, 2018).

Histological examination of the excised appendix is advisable for several reasons. Firstly, the histology should be consistent with the clinical diagnosis. Additionally, other pathologies may occasionally be found, such as carcinoid tumor, granulomas (which can be a feature of Crohn's disease or Yersinia infection), Enterobius vermicularis (pinworm) infestation, and eosinophilic infiltrates (Stringer, 2017).

In managing pain from acute appendicitis, a meta-analysis of nine randomized clinical trials revealed that opioid use did not significantly increase the risk of delayed or unnecessary surgeries in 862 adults and children with acute abdominal pain. Paracetamol and non-steroidal anti-inflammatory drugs should also be considered for pain management in patients with suspected acute appendicitis, especially those with contraindications to opioids (Snyder; Guthrie and Cagle, 2018).

Perforation is the most severe complication of acute appendicitis, potentially causing abscesses, peritonitis, bowel obstruction, fertility issues, and sepsis. Perforation rates among adults range from 17% to 32%, even with increased use of imaging, and can result in longer hospital stays, prolonged need for antibiotics, and more severe postoperative complications. A national prospective study showed that four out of 64 children (6%) with perforated appendicitis were treated with antibiotics due to suspected sepsis, even after surgery. Risk factors for perforation include advanced age, the presence of three or more comorbidities, and male sex. The time between symptom onset and diagnosis and surgery is directly associated with the risk of perforation (Snyder; Guthrie and Cagle, 2018).

REFERENCES

BAIRD, Daniel LH, *et al.* Acute appendicitis. Bmj, v. 357, 2017.

BOM, W. J.; SCHEIJMANS, J. C. G.; SALMINEN, P.; BOERMEESTER, M. A. Diagnosis of uncomplicated and complicated appendicitis in adults. Scandinavian Journal of Surgery, v. 110, n. 2, p. 170-179, 2021.

FUGAZZOLA, Paola, *et al.* The SIFIPAC/WSES/SICG/SIMEU guidelines for diagnosis and treatment of acute appendicitis in the elderly (2019 edition). World Journal of Emergency Surgery, v. 15, p. 1-15, 2020.

GUTIERREZ, Daiana, *et al.* A APENDICITE AGUDA: REVISÃO DE LITERATURA. Ensaios Usf, v. 6, n. 1, 2022.

HOFFMANN, M.; ANTHUBER, Matthias. Rational diagnostics of acute appendicitis. Der Chirurg, v. 90, p. 173-177, 2019.

IAMARINO, Ana Paula, *et al.* Fatores de risco associados às complicações de apendicite aguda. Revista do Colégio Brasileiro de Cirurgiões, v. 44, p. 560-566, 2017.

JUMAH, Soma; WESTER, Tomas. Non-operative management of acute appendicitis in children. Pediatric Surgery International, v. 39, n. 1, p. 11, 2022.

JUREMEIRA, Layane Thainá Silva, *et al*. APENDICITE AGUDA: REVISÃO DE LITERATURA. Revista Ensaios Pioneiros, v. 6, n. 1, 2022.

PEREZ, Kelly Sue; ALLEN, Steven R. Complicated appendicitis and considerations for interval appendectomy. Jaapa, v. 31, n. 9, p. 35-41, 2018.

SNYDER, Matthew J.; GUTHRIE, Marjorie; CAGLE, Stephen. Acute appendicitis: efficient diagnosis and management. American family physician, v. 98, n. 1, p. 25-33, 2018.

STRINGER, Mark D. Acute appendicitis. Journal of paediatrics and child health, v. 53, n. 11, p. 1071-1076, 2017.

TEIXEIRA, Frederico José Ribeiro, *et al.* Acute appendicitis, inflammatory appendiceal mass and the risk of a hidden malignant tumor: a systematic review of the literature. World Journal of Emergency Surgery, v. 12, p. 1-12, 2017.

TÉOULE, Patrick; LAFFOLIE, Jan; ROLLE, Udo; REISSFELDER, Christoph. Acute appendicitis in childhood and adulthood: an everyday clinical challenge. Deutsches Ärzteblatt international, v. 117, n. 45, p. 764, 2020.

WAGNER, Michel; TUBRE, Dustin John; ASENSIO, Juan A. Evolution and current trends in the management of acute appendicitis. Surgical Clinics, v. 98, n. 5, p. 1005-1023, 2018.

Chapter 10

PSYCHOTROPIC DRUG INTOXICATION

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CHAPTER 10

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Psychotropic drug intoxication is an increasing problem in emergency medicine (Sorge *et al.*, 2015). Although psychoactive drugs are beneficial in many cases of psychiatric illnesses, they also pose a risk of intoxication to patients (Pfeifer *et al.*, 2020). Reactions to intoxication vary according to

the type and dose of the substance, combined with the patient›s level of tolerance (Sorge *et al.*, 2015). Causes of intoxication are related to suicide attempts, recreational drug overdoses, and overdoses for pain relief without suicidal intent (Sorge *et al.*, 2015).

Studies report that among the psychotropics used in suicide attempts, benzodiazepines and antidepressants are the leading causes of intoxication after ICU admissions. It is also known that tricyclic antidepressants have a higher mortality rate and higher risks of severe outcomes after overdose compared to other antidepressants (Pfeifer *et al.*, 2020). Other medications, such as pregabalin, prescribed for the treatment of anxiety, seizures, and other disorders, are increasingly associated with recreational use intoxication (Isoardi *et al.*, 2020). While studies report that recreational use of pregabalin does not cause severe outcomes, it can cause sedation, hallucinations, and other symptoms (Isoardi *et al.*, 2020). Therefore, analyzing the toxicity of these drugs, the possible outcomes of their combination with other medications, and considering the patient›s history of mental disorders is very important before prescribing any medication (Pfeifer *et al.*, 2020).

Intoxication from New Psychoactive Substances (NPS) is associated with serious health problems, with symptom development ranging from central nervous system toxicity, resulting in seizures and acute psychosis, to cardiac and hepatic toxicity, causing arrhythmias and systemic failures. Severe intoxications can be fatal, especially without access to intensive care, and the lack of data on the toxicity and lethality of many NPS increases these risks (Kronstrand *et al.*, 2018). Inconsistency in the purity and composition of products containing NPS places users at high risk, as evidenced by the increase in hospital admissions and related deaths (Kronstrand *et al.*, 2018).

Synthetic opioids are the leading cause of fatal intoxications from NPS, with an increase in the abuse of fentanyl analogs since 2013. The most common lethal symptoms of opioid toxidrome include respiratory depression, pulmonary and cerebral edema. The combination of opioids with P-glycoprotein inhibitors elevates the risk of fatal complications. Synthetic cannabinoid receptor agonists also present serious risks, such as cardiovascular events and acute renal failure, although no established toxidrome exists. Synthetic cathinones and phenethylamines can cause sympathomimetic and hallucinogenic toxidromes, increasing the risk of serotonin syndrome and severe cardiovascular effects. Compared to classic drugs, NPS exhibit more severe adverse effects, with a significant increase in deaths attributed to them in recent years (Kronstrand *et al.*, 2018).

Substance abuse induces changes in neurobehavioral symptoms, which can simultaneously exacerbate liver injury. Many biochemical alterations of the liver are observed in individuals who abuse illicit or recreational drugs. The clinical characteristic of drug-induced hepatotoxicity is usually acute hepatic necrosis and markedly elevated serum aminotransferase and LDH levels with increased alkaline phosphatase (Roy; Goswami, 2016). The mechanisms involved in liver injury can be induced by some drugs of abuse and dependence, such as cocaine, amphetamine, oxycodone, heroin, nicotine, methadone,

cannabis/marijuana, fentanyl, meperidine, hydromorphone, and chemotherapeutic drugs (Roy; Goswami, 2016). Major risk factors for substance abuse include smoking, alcohol consumption, unemployment, poor education, and psychiatric disorders. Psychostimulants induce liver toxicity in a dose-dependent process, with acute or chronic use of these substances causing liver damage, hepatic steatosis, cholestatic jaundice, hepatic granulomas, hepatitis, and liver cirrhosis (Roy; Goswami, 2016). The mechanisms of drug-induced hepatotoxicity depend on reactive reactions, formation of metabolites, modification of the connections between component cells with drugs and their metabolites, activation of signaling pathways that alter apoptosis or survival mechanisms, mitochondrial damage that alters ATP formation, and cytokines modulated by these substances (Roy; Goswami, 2016).

EPIDEMIOLOGY

Psychotropic drug intoxication is a frequent public health issue in hospital emergency and urgent care departments worldwide, with alarming incidence rates. During the study period of the STRIDA Project in Sweden, which lasted approximately six years, over 2,600 patients were treated in emergency departments and ICUs with suspected psychotropic drug intoxication. There has also been an increase in mortality in the United States, involving psychotropic drugs across different age and racial groups (Helander; Bäckberg, 2018; Goldstein, 2019). Associated risk factors include male gender, age, ethnicity, psychiatric diagnosis, cardiovascular problems, obesity, smoking, alcoholism, and drug abuse (Roversi *et al.*, 2023). This highlights the need for better public health strategies and structures to address these cases.

In recent years, studies have shown an increase in the use of psychotropic drugs worldwide. In Denmark, usage among children aged 0 to 17 increased ninefold between 1996 and 2010. In Canada, there was a fourfold increase between 1998 and 2008 in individuals under 18, and similar increases in antipsychotic use were observed in the United States and the United Kingdom (Cairns et al., 2019). Mortality rates from poisoning with psychotropic drugs have increased more than prescription rates, especially for people between 45 and 64 years old. People with psychiatric diagnoses had more different compounds at the time of death compared to those without psychiatric diagnoses, with intoxication being the most frequent cause of death (40.6%), with methadone as the main intoxicant in Denmark (Reuss et al., 2021). In the UK and the European Union, mortality rates from drug and medication poisoning are notably lower than in the US (Goldstein, 2019).

In the US, there has been an increase in mortality from poisoning, suicide, and other comorbidities among white Americans over 50 years old, compared to Hispanics and blacks. These deaths occurred in urban and rural areas, mainly from poisoning. Data extracted from the CDC›s Wonder database show that age groups 25 to 74 and racial groups, especially non-Hispanic blacks, have higher chances of deaths from poisoning. People aged 55 to 74, particularly in recent years, showed a significant increase in mortality rates (Goldstein, 2019).

The incidence and prevalence of psychotropic drug intoxication have varied significantly over the years, influenced by different social, economic, and technological factors. The increase in the use of psychotropic drugs, such as antidepressants, antipsychotics, and ADHD medications, observed between 2009 and 2012 in Australia, is associated with the growth of suicidal tendencies in young people under 25 years old (Cairns *et al*., 2019). Studies indicate that young people aged 10 to 19 often intoxicate themselves with non-opioid analgesics, antipyretics, and antirheumatics due to easy access to these medications (Pawer *et al*., 2021).

There has been a significant increase in mortality rates due to intoxications with non-narcotic and psychodysleptic medications between 2000 and 2017, especially among non-Hispanic Native Americans and whites in the United States, suggesting possible misuse of medications (Goldstein, 2019). Data show that intentional drug intoxication is the leading cause of poisoning among adolescents, with an incidence rate varying from 0.4% to 10.3% internationally (Roversi *et al*., 2023). Factors such as rapid psychological, biological, and social changes increase adolescents› vulnerability to environmental stress and psychopathology.

Patients with psychiatric diagnoses present a greater variety of compounds at the time of death, indicating greater clinical complexity (Reuss *et al*., 2021). Recent technological advances, such as the increased use of the internet, social networks, and smartphones among young people, may be influencing mental health and responses to distress (Cairns *et al*., 2019). The growth of smartphone use among adolescents is correlated with increased rates of self-harm, possibly due to an increase in mental illnesses in this population or changes in behavioral responses.

Although controversial, the internet can benefit young people by promoting positive mental health and well-being strategies through new means of communication (Cairns *et al*., 2019). In British Columbia, resources such as Kids Help Phone and YouthinBC Online Chat encourage the sharing of ideas with trusted adults (Pawer *et al*., 2021). However, individuals who do not seek help have an elevated risk of self-poisoning, especially in regions with limited access to mental health services.

The implementation of programs such as the Self-Injury Signs Program (SOSI) in secondary schools can be an effective strategy to reduce self-harm events (Pawer *et al*., 2021). This cost-effective workshop, aligned with the BC Coroner›s recommendation to incorporate emotional learning and well-being strategies into the school environment, can reach a vast audience of children and young people, regardless of socioeconomic status. In summary, changes in the incidence and prevalence of psychotropic drug intoxication are influenced by a combination of social, economic, technological, and public health factors. Multifaceted approaches, including prevention, education, and social support, are essential to mitigate these public health issues (Pawer *et al*., 2021).

Adolescence is a developmental stage marked by rapid psychological, biological, and social changes. These changes can significantly contribute to the vulnerability of young people to a variety of risk factors that can lead to self-harming behaviors, including suicide, self-intoxication, and non-suicidal self-injury (NSSI). In this chapter, we explore the known risk factors for these conditions, categorizing them into genetic, environmental, socioeconomic, and lifestyle factors.

Among genetic factors, a family history of NSSI stands out as an important predictor. Adolescents with a family history of self-harm have a significantly higher prevalence of NSSI, reaching 15% compared to 8% among those without such a history, suggesting a possible genetic predisposition or, alternatively, the impact of a family environment where self-harming behaviors are more common (Pawer *et al.*, 2021).

Environmental factors play a crucial role in the development of self-harming behaviors among adolescents. Exposure to violence, whether domestic or school-related, is one of the strongest predictors of NSSI, with a prevalence of 16% among young people exposed to such forms of violence, compared to 7% among those not exposed (Pawer *et al.*, 2021). Additionally, the phenomenon of self-harm contagion, where exposure to self-harming behaviors leads to imitation, is well-documented and amplified by the increasing use of social media (Cairns *et al.*, 2019).

The COVID-19 pandemic has also brought new challenges. Repeated exposure to information about the pandemic has been identified as a risk factor for anxiety, exacerbating mental health problems among adolescents (Roversi, 2023).

The socioeconomic status (SES) of a family is a significant determinant of NSSI prevalence among adolescents. Young people from families with low annual income (<30,000 SEK) have a prevalence of 12% of NSSI, compared to 9% among those from middle-income families (30,000-60,000 SEK) and 7% among those from high-income families (>60,000 SEK) (Pawer et al., 2021). Parental education level is also a determining factor: adolescents whose parents have only primary education have a prevalence of NSSI of 13%, while those with parents who have higher education have a prevalence of 6% (Pawer *et al.*, 2021).

Furthermore, material deprivation, defined as the lack of basic resources and comfort, is strongly associated with NSSI. Adolescents living in areas of high material deprivation have a prevalence of NSSI of 14%, compared to 6% in areas of low deprivation (Pawer *et al.*, 2021). This data emphasizes the need for public policies aimed at reducing socioeconomic inequality as a form of preventive intervention.

The lifestyle of adolescents also significantly influences the risk of self-harming behaviors. Substance abuse, including over-the-counter medications like acetaminophen and ibuprofen, is common in cases of self-intoxication. Acetaminophen, due to its wide availability, is frequently the most used substance in self-intoxications (Reuss, 2020; Cairns *et al.*, 2019).

Parental mental health is another critical factor. Adolescents whose parents have a history of mental health problems have a prevalence of NSSI of 14% (Pawer *et al.*, 2021).

Additionally, the increased use of psychotropic medications, such as antidepressants and antipsychotics, especially among young people, has been notable. Among children aged 10 to 14, the use of antidepressants like fluoxetine is particularly high (Cairns *et al*., 2019).

DIAGNOSIS

To obtain a diagnosis of psychotropic drug intoxication, it is necessary to relate clinical events considering the toxicokinetics of the substances, which can present with distinct signs and symptoms. This is a fundamental factor in determining the medication and antidote to be used (Sacre *et al*., 2017). Early diagnosis is crucial in emergency services to reverse acute intoxication, as these services often have the first contact with patients in mental distress using psychotropic substances, often in suicide attempts through intentional poisoning, with adolescents being the most affected group (Perera *et al.*, 2018).

Among the most frequently marketed medications in most countries are benzodiazepines, which, when metabolized, release two active compounds: nordazepam and oxazepam. Intoxication by nordazepam primarily manifests as drowsiness and mental confusion, with other possible symptoms including gait disturbances, dizziness, hypotonia, nausea, and vomiting, even when ingested in doses up to 45 times the maximum daily dose (Sacre *et al*., 2017).

In intoxication caused by oxazepam, the most severe signs and symptoms include coma and decreased consciousness, as well as hypotonia, hypotension, and tachycardia. These symptoms can appear in doses 26 times higher than the maximum recommended dose, requiring greater attention from emergency services due to their severity at lower doses compared to nordazepam (Sacre *et al*., 2017). For early diagnosis, it is essential to identify the time of ingestion, understand the half-life of each medication, and relate the doses to the magnitude of effects. This underscores the importance of early diagnosis for reversing intoxication (Sacre *et al.*, 2017; Perera *et al.*, 2018).

Recent advances in the diagnosis of psychotropic intoxication include the development of a rapid and sensitive method: Liquid Chromatography Coupled to Mass Spectrometry (LC-MS/MS). This method allows the quantification and identification of 12 different types of psychotropic drugs and their metabolites in hair. The hair test has proven promising due to its ability to identify low doses, continuous exposures, short- and long-term exposures, and it is a non-invasive examination (Ji *et al*., 2019).

LC-MS/MS has high sensitivity, allowing the detection of extremely low doses (pg/mg levels) and the identification of various medications, including quetiapine, clozapine, paroxetine, clonazepam, midazolam, and ketamine (Ji *et al.*, 2019). Due to the lipophilic nature of these medications, there is greater accumulation in hair, facilitating rapid identification by passive diffusion and binding to hair keratin. This method can quantify and qualify medications in hair samples taken between 5 minutes and 6 hours after drug

administration, proving to be an innovation for the diagnosis of acute intoxication by quetiapine and other drugs, especially when other biological matrices are not available (Ji *et al.*, 2019).

In cases of psychotropic intoxication, early diagnosis and identification of the drug of abuse are essential for the outcome of the acute condition, as they guide therapeutic conduct and symptom management, control the progression of damage caused by toxicity, and improve prognosis. In cases of poly-consumption of psychotropic drugs, the identification of administered drugs is more challenging due to the limited ability to associate clinical signs and intoxication severity (Muñiz *et al.*, 2023).

The use of psychoactive substances can result in severe central and peripheral adverse effects and even death. Therefore, a detailed understanding of the mechanism of action of each substance helps assess potential neurological consequences and the risk of neurotoxicity (Rudin; Liechti; Luethi, 2021). The signs and symptoms of intoxications vary depending on the substance involved, the amount ingested, and the time elapsed since ingestion.

Table 1. Common signs and symptoms in each class of psychotropics:

Class	**Common Symptoms**
Antidepressants	Seizures, delusions, disorientation, confusion, hallucinations, incoherent speech, agitated and erratic behavior, cardiac arrhythmia, tachycardia, bradycardia, QT interval prolongation on ECG, hypotension, dizziness, syncope, cold skin, sweating, circulatory shock, nausea, vomiting, paralytic ileus.
Antipsychotics	Delusions, disorientation, confusion, hallucinations, incoherent speech, agitated and erratic behavior, cardiac arrhythmia, tachycardia, bradycardia, QT interval prolongation on ECG, hypotension, dizziness, syncope, cold skin, sweating, circulatory shock, neuroleptic malignant syndrome, severe muscle pain, weakness, reddish-brown urine.
Anxiolytics	Sedation, coma, seizures, respiratory depression, hypothermia.
Hypnotics	Sedation, coma, seizures, respiratory depression, slowed breathing, cyanosis, respiratory failure, hypothermia.
Stimulants	Agitation, psychosis, hyperactivity, perceptual distortions, extreme anxiety, paranoia, seizures, cardiac arrhythmia, tachycardia, bradycardia, QT interval prolongation on ECG, hypertension, severe headache, epistaxis, stroke, muscle rigidity, rhabdomyolysis, severe muscle pain, weakness, reddish-brown urine, hyperthermia.
Hallucinogens	Agitation, psychosis, hyperactivity, perceptual distortions, extreme anxiety, paranoia.
Opioids	Sedation, coma, respiratory depression, slowed breathing, cyanosis, respiratory failure, nausea, vomiting, paralytic ileus.

Despite the development of various prognostic scoring systems, such as the Simplified Acute Physiology Score (SAPS) and the Acute Physiology and Chronic Health Evaluation (APACHE), these systems may not be suitable for acutely intoxicated patients. Loss of consciousness upon arrival is significant in determining the final score but has little

impact on the outcome of intoxication, making them less sensitive in predicting mortality (Hamdi et al., 2016). Blood gas analysis is frequently performed in cases of acute poisoning as part of the clinical assessment to check the condition of patients (Hamdi *et al.*, 2016). In the present study, significantly increased mortality rates were demonstrated in patients with primary respiratory alkalosis or severe metabolic acidosis, suggesting that blood gas analysis can be useful in the early assessment of survival in cases of acute poisoning (Hamdi *et al.*, 2016).

A lower survival rate was observed in patients with primary respiratory alkalosis or severe metabolic acidosis. The findings indicated an independent statistical association between these acid-base disorders and mortality rate. Therefore, interpreting blood gases not only facilitates diagnosis but also provides indications for determining prognosis and helps identify patients requiring special intensive care. Although the direct role of acidosis in clinical outcomes remains uncertain, it has been identified as a predictor of negative outcomes in critically ill patients. Similar to other studies, it was observed that many patients with unfavorable outcomes had some component of metabolic acidosis (Hamdi *et al.*, 2016).

TREATMENT

The importance of effective treatment for psychotropic drug intoxication is crucial, given the significant increase in the use of these substances and the high risk of severe and fatal adverse effects. Social development and increased mental stress have led to the excessive use of psychotropic medications, resulting in poisonings and various health impairments that affect patients› quality of life (Ghannoum *et al.,* 2015).

Therapeutic approaches to psychotropic intoxication vary depending on the substance involved. However, initial patient stabilization is a priority, ensuring patent airways, respiratory and cardiovascular support, and gastrointestinal decontamination with activated charcoal and gastric lavage, if appropriate (Ghannoum*et al.,* 2015; Lavonas; Buchanan, 2015; Yang *et al.,* 2018).

Among the main medications frequently associated with intoxication are carbamazepine, quetiapine, valproic acid, and lithium. Overdose with carbamazepine can cause choreiform movements, ataxia, and pulmonary edema, as well as central nervous system depression, seizures, and respiratory depression (Yang *et al.,* 2018). Lithium intoxication can result in symptoms such as extrapyramidal syndrome, cerebellar alterations, and cardiac conduction irregularities (Lavonas; Buchanan, 2015). Overdose of valproic acid can cause cerebral edema, hemodynamic shock, and laboratory abnormalities, including hypernatremia, thrombocytopenia, and hypokalemia (Ghannoum *et al.,* 2015).

Supportive measures and patient monitoring are crucial in cases of overdose with carbamazepine, quetiapine, and lithium, as these medications do not have specific antidotes. However, valproic acid intoxication can be treated with the specific antidote

L-carnitine (Reuchsel; Gonnert, 2022; Lavonas; Buchanan, 2015; Ghannoum *et al.,* 2015). For all cases, it is essential to ensure a patent airway and consider the use of activated charcoal and gastric lavage as indicated.

New therapeutic approaches are being explored to improve the management of psychotropic intoxication. Hemodialysis has been studied as a potential intervention for severe cases of lithium intoxication, improving the elimination of the drug from the body. Studies indicate that hemodialysis can be effective, although there is no absolute consensus on its indication in all cases (Lavonas; Buchanan, 2015; Gosselin *et al.,*2016).

The use of hemodialysis and other extracorporeal elimination techniques has shown promise in reducing serum lithium levels and improving clinical outcomes in severe intoxications. However, it is essential to evaluate each case individually to determine the best therapeutic approach (Lavonas; Buchanan, 2015; Gosselin *et al.,* 2016). Personalizing treatment is crucial to optimizing therapeutic outcomes. Continuous evaluation of the patient›s clinical status and adjustment of interventions based on individual response are fundamental to effective management of psychotropic intoxication (Ghannoum *et al.,* 2015).

Multidisciplinary collaboration is essential for the successful treatment of psychotropic intoxication. Teams that include toxicologists, psychiatrists, pharmacists, and emergency professionals can offer a holistic approach, ensuring comprehensive patient care (Yang *et al.,* 2018). Proper management of toxicities is vital for patient recovery. Careful monitoring and rapid intervention in cases of complications such as cardiac arrhythmias and respiratory depression are crucial to minimizing adverse effects and improving prognosis (Ghannoum et al., 2015).

Challenges in treating psychotropic intoxication include the precise identification of the involved substance, management of polysubstance use symptoms, and rapid adaptation to patient needs. Ongoing development of diagnostic and treatment methods is necessary to overcome these difficulties and improve clinical outcomes (Reuchsel; Gonnert, 2022). Continuous research and development of new therapies, such as hemodialysis for lithium intoxication, promise to further improve the effectiveness and safety of psychotropic intoxication treatment. The implementation of new technologies and personalized approaches will continue to evolve, offering better prognoses for patients (Lavonas; Buchanan, 2015; Gosselin *et al.,* 2016).

REFERENCES

BAUMGARTNER, Kevin; DOERING, Michelle; SCHWARZ, Evan. Vilazodone poisoning: a systematic review. **Clinical Toxicology**, v. 58, n. 5, p. 360-367, 2020.

CAIRNS, Rose, *et al*. Trends in self-poisoning and psychotropic drug use in people aged 5–19 years: a population-based retrospective cohort study in Australia. **BMJ open**, v. 9, n. 2, p. e026001, 2019.

ĐORĐEVIĆ, Snežana, *et al*. Olanzapine poisoning in patients treated at the National Poison Control Centre in Belgrade, Serbia in 2017 and 2018: a brief review of serum concentrations and clinical symptoms. **Arhiv za higijenu rada i toksikologiju**, v. 73, n. 2, p. 126-130, 2022.

GHANNOUM, Marc, *et al*. Extracorporeal treatment for valproic acid poisoning: systematic review and recommendations from the EXTRIP workgroup. **Clinical Toxicology**, v. 53, n. 5, p. 454-465, 2015.

GOLDSTEIN, Edward. Rise in mortality involving poisoning by medicaments other than narcotics, including poisoning by psychotropic drugs in different age/racial groups in the US. **Plos one**, v. 14, n. 7, 2019.

GOSSELIN, Sophie, *et al*. Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning. **Clinical Toxicology**, v. 54, n. 10, p. 899-923, 2016.

HAMDI, Haleh, *et al*. Acid-base disturbances in acute poisoning and their association with survival. **Journal of critical care**, v. 35, p. 84-89, 2016.

HELANDER, Anders; BÄCKBERG, Matilda. Epidemiology of NPS based confirmed overdose cases: The STRIDA project. **New Psychoactive Substances: Pharmacology, Clinical, Forensic and Analytical Toxicology**, p. 461-473, 2018.

ISOARDI, Katherine Z., *et al*. Pregabalin poisoning and rising recreational use: a retrospective observational series. **British journal of clinical pharmacology**, v. 86, n. 12, p. 2435-2440, 2020.

JI, Jiao-jiao, *et al*. An LC–MS/MS method for the simultaneous determination of 12 psychotropic drugs and metabolites in hair: Identification of acute quetiapine poisoning using hair root. **Forensic science international**, v. 301, p. 341-349, 2019.

KRONSTRAND, Robert, *et al*. Fatal poisonings associated with new psychoactive substances. **New Psychoactive Substances: Pharmacology, Clinical, Forensic and Analytical Toxicology**, p. 495-541, 2018.

KUMMER, Mirjam, *et al*. Characteristics of presentations to the emergency department following attempted suicide with drugs. **International journal of environmental research and public health**, v. 18, n. 19, p. 10232, 2021.

LAVONAS, Eric J.; BUCHANAN, Jennie. Hemodialysis for lithium poisoning. **Cochrane Database of Systematic Reviews**, n. 9, 2015.

MUÑIZ, Gomila, *et al*. Ketamine detection in urine samples from patients poisoned by recreational drugs: epidemiologic, clinical, and toxicologic profiles. **Emergencias**, v. 35, p. 6-14, 2023.

PAWER, Samantha, *et al*. Analyses of child and youth self-poisoning hospitalizations by substance and socioeconomic status. **International journal of environmental research and public health**, v. 18, n. 13, p. 7003, 2021.

PERERA, Jayashanki, *et al*. Presentations to NSW emergency departments with self-harm, suicidal ideation, or intentional poisoning, 2010–2014. **Medical journal of Australia**, v. 208, n. 8, p. 348-353, 2018.

PFEIFER, Philippe, *et al*. A comprehensive analysis of attempted and fatal suicide cases involving frequently used psychotropic medications. **General hospital psychiatry,** v. 63, p. 16-20, 2020.

REUCHSEL, Caterina; GONNERT, Falk A. Successful treatment of severe quetiapine intoxication with CytoSorb hemoadsorption. **Journal of Clinical Pharmacy and Therapeutics**, v. 47, n. 9, p. 1471-1474, 2022.

REUSS, Christian Fyhn, *et al.* Increased risk of fatal intoxication and polypharmacy among psychiatric patients at death. **Journal of forensic sciences**, v. 66, n. 1, p. 255-264, 2021.

RIETJENS, Saskia J., *et al*. Pregabalin poisoning: Evaluation of dose-toxicity relationship. **British journal of clinical pharmacology**, v. 88, n. 3, p. 1288-1297, 2022.

ROVERSI, Marco, *et al*. Drug self-poisoning in adolescents: A report of 267 cases. **Toxicology reports,** v. 10, p. 680-685, 2023.

ROY, Dijendra Nath; GOSWAMI, Ritobrata. Drugs of abuse and addiction: A slippery slope toward liver injury. **Chemico-biological interactions**, v. 255, p. 92-105, 2016.

RUDIN, Deborah; LIECHTI, Matthias E.; LUETHI, Dino. Molecular and clinical aspects of potential neurotoxicity induced by new psychoactive stimulants and psychedelics. **Experimental neurology**, v. 343, p. 113778, 2021.

SACRE, L., *et al*. Toxicodynetics in nordiazepam and oxazepam overdoses. In: Annales Pharmaceutiques Francaises. **Elsevier Masson,** 2017. p. 163-171.

SORGE, M., *et al*. Self-poisoning in the acute care medicine 2005-2012. **Anaesthesist**, v. 64, n. 6, 2015.

YANG, Xiangming, *et al*. Early hemoperfusion for emergency treatment of carbamazepine poisoning. **The American Journal of Emergency Medicine**, v. 36, n. 6, p. 926-930, 2018.

Chapter 11

SUICIDAL BEHAVIOR IN THE EMERGENCY ROOM

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CHAPTER 11

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Suicidal behavior is a global public health concern, responsible for 1.4% of all deaths, amounting to approximately 800,000 deaths annually (Klonsky, May & Saffer, 2016). Suicide is the fifteenth leading cause of death worldwide and the nineteenth leading cause of the global burden of disease, particularly prevalent in developed countries and among men (Klonsky; May and Saffer, 2016). The Centers for Disease Control and Prevention

(CDC) defines suicide as death caused by self-directed behavior with the intent to die, while a suicide attempt is a non-fatal self-directed behavior that can be harmful, and suicidal ideation refers to thinking about or planning suicide (Klonsky; May and Saffer, 2016).

Research on suicide faces challenges such as diverse definitions and terminologies without consensus, differing measures, stigma, and the complexity of suicidal thoughts and behaviors (Klonsky; May and Saffer, 2016). In clinical evaluation, tools like the Suicide Attempt and Self-Injury Interview and the Suicidal Ideation Scale are used to better understand these behaviors and thoughts (Klonsky; May and Saffer, 2016). Clinical interventions include Dialectical Behavior Therapy and Cognitive Therapy for suicide prevention, although no universally accepted gold standard exists (Klonsky; May and Saffer, 2016). Suicide prevention can also be addressed through means restriction, medical education, and school programs (Klonsky; May and Saffer, 2016).

The transition to emerging adulthood is characterized by exploration and significant changes, being a period of high exposure and vulnerability to risk factors such as drug use and unprotected sex (Pereira *et al.*, 2018). Protective factors, such as self-esteem and self-efficacy, as well as a well-structured support network, help mitigate these risks and promote better problem-solving abilities (Pereira *et al.*., 2018). Effective interventions during this phase are essential for developing a healthy mindset and reducing the risk of suicide (Pereira *et al.*, 2018).

Active interventions and post-discharge follow-up have shown relevance in reducing new suicide attempts in patients admitted to emergency and urgent care services (Inagaki *et al.*, 2019). Approaches that include recurring contact with patients and care coordination are crucial for preventing suicidal behavior (Inagaki*et al.*, 2019).

Studies indicate that neurocognitive functioning can predict suicidal behavior in young people with affective disorders, suggesting that detailed neurocognitive assessments can be useful in identifying and preventing suicidal behaviors (McHugh *et al.*, 2020). Additionally, elevated levels of impulsivity have been associated with a higher likelihood of suicide attempts, highlighting the importance of assessing impulsivity in preventing suicidal behavior (Millner*et al.*, 2018).

Research on suicide biomarkers in the past five years has been promising, with the identification of potential biomarkers that can predict risk and classify diagnostic subtypes, enabling more precise and effective interventions (Johnston *et al.*, 2020). These advances could revolutionize how suicide risk is assessed and treated in daily clinical practice.

EPIDEMIOLOGY

Suicidal behavior in psychiatric emergencies represents a significant challenge for mental health professionals and emergency care systems. This complex phenomenon is characterized by the manifestation of suicidal behaviors, including suicidal ideation, suicide

attempts, and self-harming behaviors, which require immediate and effective interventions to mitigate the risk of morbidity and mortality (Gaynor *et al.*, 2023).

According to current data, suicide accounts for approximately 1.4% of all global deaths, resulting in more than 800,000 annual fatalities. When considered together, suicide and suicidal behavior constitute the nineteenth leading cause of global disease burden. Impulsivity plays an instrumental role in suicide, as suicidal behaviors are often executed by impulsive decisions with little prior assessment of harmful consequences. Individuals with a higher propensity for impulsivity who contemplate suicide are considered at greater risk of actualizing these thoughts (Millner *et al.*, 2018).

The lifetime prevalence rates of suicidal ideation and suicide attempts are approximately 9.2% and 2.7%, respectively. The risk of repeated suicide attempts is particularly high in the period following the first attempt, with one in ten patients reattempting within five days. In England, 220,000 patients are admitted annually for self-harming behaviors (Inagaki *et al.*, 2019).

Studies highlight interventions aimed at reducing suicidal behaviors and ideation in adolescents, a particularly vulnerable group. Recent data indicate that suicide is the second leading cause of death among adolescents in some countries, second only to automobile accidents. This suggests a continuous need for preventive strategies tailored to the specific demographic and psychosocial characteristics of adolescents (Gaynor *et al.*, 2023).

Moreover, significant gender differences in suicide, suicidal ideation, and self-harm have been observed after release from correctional institutions. A higher proportion of completed suicides was found among women in these circumstances, underscoring the importance of differentiated approaches for men and women in the post-incarceration context (Janca *et al.*, 2023).

During the COVID-19 pandemic, there was a concerning increase in self-harm and suicidal behaviors among children and young people, exacerbated by prolonged exposure to precipitating factors. This increase reflects the adverse effects of public health crises on the mental health of the young population, with a potential rise in psychiatric emergencies (López *et al.* 2023).

Ross *et al.* (2023) highlight that presentations in emergency departments with suicidal ideation and self-harm represent missed opportunities for effective preventive interventions. The need for rapid screening and intervention protocols is emphasized to identify and intervene early in high-risk cases, highlighting the importance of a multifaceted approach in psychiatric emergencies that integrates epidemiological research, early identification of risk factors, and continuous development of intervention strategies.

Understanding the complexities of suicidal behavior is crucial for improving care and reducing the devastating impacts on communities. This study aims to investigate and comprehend the prevalence, incidence, risk factors, and current trends associated with suicidal behaviors, including suicidal ideation, suicide attempts, and self-harm. Additionally,

it seeks to analyze the opportunities and challenges in early and effective intervention of these behaviors in different populations, considering demographic, contextual, and temporal variations, contributing to the development of preventive strategies and clinical interventions that can reduce the impact of suicidal behavior on public health and improve the management of these cases in psychiatric emergency services (Millner*et al.,* 2018; Inagaki *et al*., 2019; Gaynor *et al*., 2023; Janca *et al*., 2023; López *et al*., 2023; Ross *et al*., 2023).

According to Ross *et al.* (2023), suicidal ideation, a factor that frequently precedes suicidal behaviors such as unsuccessful suicide attempts or completed suicides, is a globally prevalent phenomenon affecting approximately 9% of the population over their lifetime. In a study conducted by the authors involving 1,662,118 individuals aged over 10 years, 15,267 presented with suicidal ideation in the emergency room during the study period.

The prevalence of suicidal behaviors also varies among population groups within the same region. Young people, especially LGBTQ+ adolescents, face disproportionately high rates of suicidal ideation and suicide attempts, often related to stigma, bullying, and lack of family support. Similarly, ethnic minority groups may encounter additional barriers to accessing culturally sensitive mental health care, increasing the risk of undetected or inadequately treated suicidal crises. In this regard, a study conducted by Janca *et al.* (2023) aimed to synthesize evidence on the incidence of suicide, suicidal ideation, and self-harm after release from incarceration, with a focus on gender differences. The analysis included 29 studies. The crude mortality rate (CMR) for suicide per 100,000 person-years was 114.5 (95% CI 97.0, 132.0) for samples not stratified by gender, 139.5 (95% CI 91.3, 187.8) for women, and 121.8 (95% CI 82.4, 161.2) for men. The standardized mortality ratio (SMR) for suicide was 7.4 (95% CI 5.4, 9.4) for samples not stratified by gender, 14.9 for women (95% CI 6.7, 23.1), and 4.6 for men (95% CI 1.3, 7.8). The pooled incidence rate ratio (IRR) comparing suicides between women and men was 1.1 (95% CI 0.9, 1.4). According to the authors, the suicide rate is higher after release than during incarceration, with the elevated risk for women being three times greater than for men compared to the general population (Janca *et al.,* 2023).

López-Goñi et al. (2020), in turn, introduced significant contributions to the topic by conducting a prospective multicenter case-control study investigating the incidence of suicidal behavior in a sample of 440 patients seen in psychiatric emergency services. Using the Brugha Adverse Life Events Scale and the Columbia Suicide Severity Rating Scale, the authors divided the patients into three groups: those with no previous suicide attempts, those with a single index attempt, and those with multiple attempts. After two years, medical histories were reviewed to analyze the occurrence of suicidal behavior.

DIAGNOSIS

Suicide represents a serious global public health problem. WHO statistics indicated nearly 800,000 deaths by suicide annually, with projections of 1.53 million by 2020. However, the true extent of the problem is reflected in the widespread underreporting in most countries. It is estimated that the number of suicide attempts is significantly higher, between 10 to 20 times, compared to the number of completed suicides. A previous history of suicide attempts has been the best predictor of subsequent completed suicides, with a repetition rate of 35% to 50% within this group. Therefore, early detection and effective intervention are crucial for preventing new attempts. However, the lack of official data due to methodological challenges corroborates the difficulty in obtaining an accurate understanding of this problem (Espandian *et al.*, 2020).

To introduce the topic of suicide diagnosis in the emergency room, it is crucial to highlight the severity of suicidal behavior as a significant public health issue, especially among children and adolescents. The alarming increase in cases of suicidal ideation and suicide attempts in this age group underscores the urgent need to identify early risk factors (Servi *et al.*, 2023). Suicide attempt (SA) behavior and non-suicidal self-injury (NSSI) among these individuals are becoming increasingly prevalent and represent a serious challenge for mental health. Suicide is the leading cause of death in this age group, and both SA and NSSI have profound impacts on families, communities, and generate significant social costs (Kim; Ryu and Kim, 2020).

These behaviors are frequent reasons for presentation in child and adolescent psychiatric emergencies, with NSSI being particularly common. Pediatric emergency departments (PED) play a crucial role in screening and referring for specialized psychiatric treatment, given the high incidence of these issues. This demonstrates how early and properly documented diagnosis can lead to better treatment outcomes and the implementation of preventive measures (Kim; Ryu and Kim, 2020). It is worth noting that the use of advanced statistical techniques and artificial intelligence has shown promise in predicting suicidal behaviors and aiding in the implementation of preventive strategies and specific therapeutic interventions (Servi *et al.*, 2023).

Accurate diagnosis of suicide represents a significant challenge in emergency services. Reliable allocation of International Classification of Diseases, 10th Revision (ICD-10) codes for suicide and self-harm attempts in emergency departments (EDs) is crucial for monitoring treatment effectiveness and improving health outcomes. However, studies highlight inadequate sensitivity of these codes in accurately identifying suicide cases, resulting in underestimation of the true prevalence and impact of these events in the treated population (Sveticic; Stapelberg and Turner, 2020).

Suicide risk assessment in the emergency room is a critical and challenging process for mental health professionals. Various instruments have been developed to facilitate this

assessment. Some have demonstrated significant variations in diagnostic accuracy, with some tools presenting high sensitivity but low specificity, and vice versa. Despite many of these instruments being widely used, none have achieved sufficient diagnostic accuracy to be considered entirely reliable in predicting suicide or suicide attempts. This underscores the need for a comprehensive clinical evaluation and cautious use of risk assessment tools, considering their limitations and the specific context of each patient. Thus, the importance of an integrated approach that combines clinical experience with careful use of assessment tools is emphasized, ensuring that preventive interventions are based on a complete understanding of the patient (Runeson *et al.*, 2017).

Suicidal behavior can present in different forms: suicidal ideation, suicide attempts, and completed suicide. Suicidal ideation includes active or passive thoughts and behaviors such as threats, preparatory acts, and interrupted or aborted suicide attempts. A suicide attempt can be described as self-harming behavior with the intention to die, which may or may not be completed (Sveticic; Stapelberg and Turner, 2020). Previous studies have shown that approximately 60% of suicidal thoughts become attempts within one year of the onset of ideation. Therefore, the appropriate approach to suicidal ideation in the emergency room is of utmost importance, as it is a significant risk factor for suicide (Ana-Isabel *et al.*, 2021).

It should be reinforced that suicidal behavior is a multifaceted and complex phenomenon. Complaints such as mood disturbance, altered mental state, neurological symptoms, anxiety, agitation, exposure to drugs, and toxic agents may be present (Sveticic, Stapelberg, Turner, 2020). Characteristics such as impulsivity and hopelessness reinforce the risk of suicide attempts (Ana-Isabel *et al.*, 2021).

The Integrated Motivational-Volitional (IMV) model of suicidal behavior considers suicide as a behavioral process divided into three phases. In the pre-motivational phase, the model describes the biopsychosocial context in which suicidal ideation and behavior may arise. The motivational phase addresses the factors that lead to the emergence of suicidal ideation, and the volitional phase focuses on the factors that govern the transition from suicidal ideation to suicide attempts and death by suicide. While the IMV offers a useful framework, it has limitations, such as representing suicide in a linear manner, ignoring the cyclical nature of suicidal behavior, where individuals may transition between phases repeatedly. Additionally, it does not adequately consider repetitive suicidal behavior, which is associated with higher levels of distress than cases with only one episode. To address these limitations, it is necessary to develop a more comprehensive model that contemplates all possible combinations and variables. Emerging statistical techniques, such as network analysis, offer new opportunities to investigate variations in risk trajectories in different populations and optimize the efficiency of suicidal ideation and behavior assessment measures without compromising accuracy (Espandian *et al.*, 2020).

Additionally, among the common reasons for admission to psychiatric emergency services, beyond suicidal behavior, is non-suicidal self-injury (NSSI), defined as deliberate

self-inflicted harm to one›s body without the intention to end one›s life. In a study conducted among patients admitted to an emergency service, 26 out of 30 patients who attempted suicide had a history of self-injury in the past. Thus, it is evident that both non-suicidal self-injury and suicide attempts are risk factors for each other. Therefore, it is crucial for physicians to be adept at crisis intervention and refer patients to mental health services when appropriate (Kim; Ryu and Kim, 2020).

Recent studies highlight the analysis of biomarkers as tools for diagnosing suicidal behavior. In the study by Fernández-Sevillano *et al.* (2022), plasma levels of various cytokines, including IL-2, IL-4, IL-6, and TNF-a, were analyzed in patients with a recent suicide attempt, patients with a history of suicide attempts, patients with major depressive disorder (MDD) without a history of attempts, and healthy controls. The results indicated that IL-6 levels were significantly elevated in patients with recent and past suicide attempts compared to MDD patients who had not attempted suicide, suggesting that elevated IL-6 levels may be associated with traumatic experiences and stress, negatively impacting attention and increasing the risk of suicide (Fernández-Sevillano *et al.*, 2022).

Moreover, the assessment of cognitive function and overall functioning is essential for identifying suicide risk. The study found that elevated IL-6 levels were correlated with poorer attention performance and lower global functioning scores, indicating that immunological dysfunctions may contribute to the vulnerability to suicidal behavior. Therefore, the evaluation of inflammatory biomarkers can be a valuable complement to clinical screening, helping to identify high-risk patients and guiding more effective preventive interventions (Fernández-Sevillano *et al.*, 2022).

TREATMENT

Once admitted to an emergency service, patients with suicidal ideation face the first challenge in managing their condition. In many countries, including Brazil, there are still no standardized measures to determine whether a patient is fit for discharge. The global tendency is that, once the emergency condition is resolved, the individual is released from hospital care. Thus, discharge depends solely on the attending physician›s opinion about the patient›s acute condition, without considering their mental situation as a whole (Katz *et al.*, 2020).

The conventional treatment for suicidal behavior in emergency and urgent care settings involves a multifaceted approach that includes rapid stabilization, comprehensive assessment, and appropriate patient disposition. Emergency departments have seen a significant increase in visits for mood disorders, including severe depression and suicidal ideation, necessitating effective interventions to manage these crises. Effective management of acute suicidal behavior, including suicidal ideation and suicide attempts, is crucial for patient survival. Besides cognitive-behavioral therapies, there is limited evidence on the

effectiveness of psychosocial interventions in reducing suicidal behavior rates. Studies indicate that interventions such as psychosocial assessment, hospital admission, or referral for outpatient follow-up can reduce the recurrence of suicidal behaviors and suicide mortality. However, negative attitudes and stigma from healthcare staff can negatively impact patient engagement and their willingness to seek help (Hill *et al.*, 2019).

However, it is known that the risk of death by suicide is highest within the first year after an attempt. Patients with suicidal ideation require long-term medical follow-up, with the period immediately after discharge being crucial for appropriate interventions. It is recommended that the patient be maintained in a safe environment and constantly accessed by the healthcare team. However, few care units worldwide provide psychologists, occupational therapists, psychiatrists, and other professionals capable of assisting a suicidal patient full-time, causing many to lose follow-up within the first year of the attempt (Hill *et al.*, 2019).

After discharge from the emergency service, many patients who attempted suicide receive prescriptions for antidepressants, especially selective serotonin reuptake inhibitors (SSRIs). Although this class of medications is relatively safer due to being less toxic in overdose cases, studies suggest that SSRIs may increase self-destructive thoughts and suicidal behavior within the first month of use. Thus, while they may be beneficial in the long term, patients who start using SSRIs need to be closely monitored in the first weeks, support that is rarely provided after emergency discharge (Katz *et al.*, 2020).

Another pharmacological option is lithium, widely used in the management of mood disorders due to its anti-suicidal properties. Despite being a viable alternative, lithium is rarely prescribed after emergency discharge due to the lack of experience of non-psychiatric physicians. The therapeutic dose of lithium is close to its toxic dose, requiring outpatient follow-up of the patient, which often does not occur (Katz *et al.*, 2020). Observational studies indicate that regions with higher natural lithium concentrations in water have lower suicide rates. Additionally, Danish patients who continued to take lithium as prescribed had a lower risk of suicide than those who did not maintain the treatment (Bolton; Gunnel and Turecki, 2015).

Studies show that antidepressants can reduce suicidal thoughts and behaviors, but the results vary with age. Reviews indicate a reduction of 40% to 81% in suicide attempts among depressed patients using antidepressants. However, a meta-analysis revealed an increased risk of suicidal thoughts and behavior in young people under 25, while there is a protective effect for people aged 25 to 64 and those over 65 (Bolton; Gunnell and Turecki, 2015).

Various interventions have been specifically developed for patients who self-poison, including postcard interventions, telephone interventions, and brief psychological interventions. However, the effectiveness of these approaches is unclear due to inconsistencies in study methodologies and designs, making it difficult to compare results

(Inui-Yukawa *et al.*, 2021). Throughout their treatment, both within and outside healthcare services, suicidal patients encounter prejudice. Empathy is often overshadowed by judgment and the stigmatization of the individual›s mental condition. Inevitably, the lack of support from healthcare staff and the feeling of societal disregard lead to treatment abandonment (Hill *et al.*, 2019).

REFERENCES

ANA-ISABEL, De Santiago-Díaz, *et al.* Suicidal behaviour: emergency department attendance for suicidal recurrence and other psychiatric or medical reasons in the 6 months following the index episode. **Actas espanolas de psiquiatria**, v. 49, n. 6, p. 244, 2021.

BOLTON, James M.; GUNNELL, David; TURECKI, Gustavo. Suicide risk assessment and intervention in people with mental illness. **Bmj**, v. 351, 2015.

ESPANDIAN, Ashkan, *et al.* Relevant risk factors of repeated suicidal attempts in a sample of outpatients. **Revista de Psiquiatría y Salud Mental (English Edition)**, v. 13, n. 1, p. 11-21, 2020.

FERNÁNDEZ-SEVILLANO, Jessica, *et al.* Inflammation biomarkers in suicide attempts and their relation to abuse, global functioning and cognition. **The World Journal of Biological Psychiatry**, v. 23, n. 4, p. 307-317, 2022.

GAYNOR, Keith, *et al.* A meta-analysis of targeted interventions for reducing suicide-related behaviour and ideation in adolescents: Implications for trial design. **Comprehensive psychiatry**, v. 122, p. 152374, 2023.

HILL, Nicole TM, *et al.* Development of best practice guidelines for suicide-related crisis response and aftercare in the emergency department or other acute settings: a Delphi expert consensus study. **BMC psychiatry**, v. 19, p. 1-10, 2019.

INAGAKI, Masatoshi, *et al.* Active contact and follow-up interventions to prevent repeat suicide attempts during high-risk periods among patients admitted to emergency departments for suicidal behavior: a systematic review and meta-analysis. **BMC psychiatry**, v. 19, p. 1-11, 2019.

INUI-YUKAWA, Masami, *et al.* Effectiveness of assertive case management for patients with suicidal intent. P**sychiatry research**, v. 304, p. 114125, 2021.

JANCA, Emilia, *et al.* Sex differences in suicide, suicidal ideation, and self-harm after release from incarceration: a systematic review and meta-analysis. **Social psychiatry and psychiatric epidemiology**, v. 58, n. 3, p. 355-371, 2023.

JOHNSTON, Jenessa N., *et al.* Suicide biomarkers to predict risk, classify diagnostic subtypes, and identify novel therapeutic targets: 5 years of promising research. **International journal of neuropsychopharmacology**, v. 25, n. 3, p. 197-214, 2022.

KATZ, Cara, *et al.* Psychotropic medication use before and after suicidal presentations to the emergency department: a longitudinal analysis. **General hospital psychiatry**, v. 63, p. 68-75, 2020.

KIM, Harin; RYU, Jeong Min; KIM, Hyo-Won. Characteristics and trends of suicide attempt or non-suicidal self-injury in children and adolescents visiting emergency department. **Journal of Korean medical science**, v. 35, n. 33, 2020.

KLONSKY, E. David; MAY, Alexis M.; SAFFER, Boaz Y. Suicide, suicide attempts, and suicidal ideation. **Annual review of clinical psychology**, v. 12, p. 307-330, 2016.

LÓPEZ-GOÑI, José Javier, *et al.* Repetición de conductas suicidas en urgencias psiquiátricas en pacientes sin intentos previos, index y repetidores: un estudio prospectivo. **Revista de Psiquiatría y Salud Mental**, v. 13, n. 4, p. 192-201, 2020.

MCHUGH, Catherine M., *et al*. Neurocognitive functioning predicts suicidal behaviour in young people with affective disorders. **Journal of affective disorders**, v. 281, p. 289-296, 2021.

MILLNER, Alexander J., *et al.* Are suicide attempters more impulsive than suicide ideators?. **General hospital psychiatry**, v. 63, p. 103-110, 2020.

NOWLAND, Rebecca, *et al.* Management of patients with an advance decision and suicidal behaviour: a systematic review. **BMJ open**, v. 9, n. 3, p. e023978, 2019.

O›CONNOR, Rory C.; KIRTLEY, Olivia J. The integrated motivational–volitional model of suicidal behaviour. **Philosophical Transactions of the Royal Society B: Biological Sciences**, v. 373, n. 1754, p. 20170268, 2018.

PEREIRA, Anderson Siqueira, *et al*. Risk and protective factors for suicide attempt in emerging adulthood. **Ciencia & saude coletiva**, v. 23, p. 3767-3777, 2018.

QUINLIVAN, Leah, *et al*. Advance decisions to refuse treatment and suicidal behaviour in emergency care:'it›s very much a step into the unknown'. **BJPsych open**, v. 5, n. 4, p. e50, 2019.

ROSS, E., *et al*. Emergency department presentations with suicide and self-harm ideation: a missed opportunity for intervention?. **Epidemiology and psychiatric sciences**, v. 32, p. e24, 2023.

RUNESON, Bo, *et al*. Instruments for the assessment of suicide risk: A systematic review evaluating the certainty of the evidence. **PLoS one**, v. 12, n. 7, p. e0180292, 2017.

SERVI, Michaela, *et al*. Statistical and artificial intelligence techniques to identify risk factors for suicide in children and adolescents. **Science Progress**, v. 106, n. 4, p. 00368504231199663, 2023.

STEEG, Sarah,*et al.* Accuracy of risk scales for predicting repeat self-harm and suicide: a multicentre, population-level cohort study using routine clinical data. **BMC psychiatry,** v. 18, p. 1-11, 2018.

SVETICIC, Jerneja; STAPELBERG, Nicholas CJ; TURNER, Kathryn. Suicidal and self-harm presentations to emergency departments: the challenges of identification through diagnostic codes and presenting complaints. **Health Information Management Journal,** v. 49, n. 1, p. 38-46, 2020.

VÁZQUEZ-LÓPEZ, Paula, *et al.* Self-injury and suicidal behavior in children and youth population: Learning from the pandemic. 2023.

Chapter 12

HYPERTENSIVE EMERGENCIES IN PREGNANCY

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CHAPTER 12

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Hypertensive emergencies in pregnancy are one of the leading causes of maternal and fetal morbidity and mortality. They are characterized by a significant increase in blood pressure during pregnancy, responsible for about 10% of gestational complications globally, requiring immediate medical intervention. These conditions are classified into four categories according to the American College of Obstetricians and Gynecologists Taskforce on Hypertension during Pregnancy: chronic hypertension, gestational hypertension, pre-eclampsia,

and eclampsia. In the United States (USA), it is estimated that hypertensive disorders occur in approximately 1 in 9 pregnancies, with chronic hypertension complications present in 1% to 2% of deliveries and gestational hypertension in 2% to 3% of cases. Pre-eclampsia affects between 3% and 5% of pregnancies, with progression to eclampsia in 0.6% to 2%-3% of cases, depending on the severity of the initial condition (Wilkerson; Ogunbodede, 2019).

The incidence of chronic hypertension in women of childbearing age is increasing, particularly due to rising rates of obesity, diabetes mellitus, and inadequate diets. In the USA, African-American women have a higher incidence of pre-eclampsia and a threefold higher risk of fatalities compared to white women, partly due to difficulty accessing healthcare. Thus, the development of hypertensive emergencies in pregnancy involves both physiological and socioeconomic factors, emphasizing the need for adequate knowledge of the diagnosis, treatment, and possible complications of these conditions (Wilkerson; Ogunbodede, 2019).

There are important distinctions between chronic hypertension and gestational hypertension: the former occurs before pregnancy or is diagnosed before 20 weeks, while the latter is diagnosed after 20 weeks of pregnancy, with blood pressure values exceeding 140/90 mmHg (mild gestational hypertension) or 160/110 mmHg (severe gestational hypertension). Pre-eclampsia is characterized by the presence of hypertension with or without proteinuria, with possible additional signs in previously hypertensive pregnant women, including thrombocytopenia, pulmonary congestion, pulmonary edema, elevated liver transaminases, acute renal failure, and central nervous system disorders (Vadhera; Simon, 2014).

Eclampsia, defined by the occurrence of tonic-clonic seizures in pregnant women with pre-eclampsia without other causes, can occur before, during, or after delivery, with more than 90% of cases occurring after 28 weeks of gestation (Wilkerson & Ogunbodede, 2019). Delivery is considered the ideal treatment for severe cases, provided the mother is stable and the fetus is viable, usually after 34 weeks of gestation. Before this period, the aim is to stabilize the mother until the fetus is viable (Vadhera; Simon, 2014).

Hypertensive disorders in pregnancy affect between 10% and 20% of pregnancies in the United States, significantly resulting in maternal and fetal morbidity and mortality. They are also one of the main causes of postpartum readmission. Possible complications include pulmonary edema, premature placental abruption, stroke, thromboembolic events, disseminated intravascular coagulation, and multiple organ failure. The fetus is at risk of intrauterine growth restriction or even intrauterine death (Hauspurg; Jeyabalan, 2020).

According to the Department of Medicine II, Charles University in Prague, First Faculty of Medicine, there is a reduction in blood pressure (BP) during the first trimester, especially in diastolic BP (DBP), with values decreasing between 8 and 15 mmHg at weeks 20-24, due to vasodilation induced by local mediators such as prostacyclin and nitric oxide. Subsequently, the stroke volume increases between 10% and 30%, returning to

pre-gestational values by week 36. These variations can occur in both hypertensive and normotensive women. There are three main types of hypertension in pregnancy: pre-existing hypertension (diagnosed before pregnancy or up to 20 weeks and persistent after 42 days postpartum, possibly associated with proteinuria), gestational hypertension (diagnosed after 20 weeks and disappearing after 42 days postpartum), and pre-eclampsia (systemic disorder associated with significant proteinuria, >0.3g/24h). Regular attendance at health centers for BP monitoring is crucial to avoid hypertensive emergencies (Cífková, 2023).

EPIDEMIOLOGY

Despite a reduction in prevalence after years of interventions, hypertensive diseases in pregnancy remain one of the leading causes of maternal morbidity and mortality worldwide, especially in low- and middle-income countries. These conditions are responsible for approximately 14% of maternal deaths globally, with a prevalence of 116.4 per 100,000 women of reproductive age (Jiang *et al.*, 2022).

Among hypertensive diseases in pregnancy, hypertensive emergencies had a prevalence of 0.3%, while hypertensive urgencies had a prevalence of 0.9%. This shows that hypertensive urgencies are 2.5 times more common than hypertensive emergencies in emergency departments. Various subtypes of adverse organ damage caused by hypertension have been identified, including pulmonary edema/heart failure (32%), ischemic stroke (29%), acute coronary syndrome (18%), hemorrhagic stroke (11%), acute aortic syndrome (2%), and hypertensive encephalopathy (2%) (Vallelonga *et al.*, 2020).

Data from a study indicate that among hypertensive disorders of pregnancy, the adjusted prevalence of chronic hypertension ranged from 1.0% in Hawaii to 3.4% in Alaska. In the case of hypertensive disorders of pregnancy, adjusted rates ranged from 4.3% in Massachusetts to 9.3% in Louisiana. Eclampsia showed even greater variation, with adjusted prevalences ranging from 0.03% in Delaware to 2.8% in Hawaii, with four states (Hawaii; Alaska; Virginia and Alabama) showing prevalences above 1% (Butwick; Druzin; Shaw and Guo, 2020).

Another study showed that in the United States, between 10% and 20% of pregnancies are complicated by hypertensive disorders of pregnancy. These disorders are responsible for a considerable portion of maternal morbidity and mortality and are the main factor for postpartum readmission of puerperal women in the early postpartum period (Hauspurg; Jeyabalan, 2022).

About 7.4% of maternal deaths are attributable to hypertensive diseases during pregnancy, representing approximately one-fifth of prenatal hospitalizations and two-thirds of referrals to day assessment units (Jiang *et al.*, 2022). In 2017, the analysis of 3,855,500 live births in the USA revealed that the average probability of eclampsia was 2.4 times higher for a woman, depending on the state where the delivery occurred. State-level

variation in the prevalence of chronic hypertension and hypertensive disorders of pregnancy was smaller, suggesting the need for public health efforts to understand and reduce these variations (Butwick; Druzin; Shaw and Guo., 2020).

A study with 571 women investigated the development of chronic conditions after pregnancies complicated by hypertensive diseases, comparing them to 1,142 age- and parity-matched referents. Women with a history of hypertensive diseases of pregnancy had a higher risk of cardiovascular events and experienced accelerated accumulation of 16 chronic conditions, with no difference in all-cause mortality rates between the groups (Garovic et al., 2020). About 60% of women who develop late postpartum eclampsia have no previous history of hypertensive disorder during pregnancy, manifesting the first symptoms in the first 7 to 10 days postpartum, with headache being the most common symptom (Hauspurg; Jeyabalan, 2022). Furthermore, there are few national and international guidelines addressing late-onset postpartum hypertension, and existing guidelines do not clearly define the issue (Hauspurg; Jeyabalan, 2022).

Although maternal mortality is significantly lower in high-income countries (HICs) compared to low- and middle-income countries, hypertensive diseases of pregnancy are still one of the leading causes of maternal death worldwide. In the United Kingdom and Ireland, the proportion of maternal deaths from these diseases was 2.8% between 2011 and 2013, while maternal mortality associated with these conditions ranged between 0.08 and 0.42 per 100,000 pregnancies from 2009 to 2015 (Jiang *et al*., 2022).

Regionally, Africa recorded the highest prevalence of hypertensive diseases of pregnancy, with an average of 334.9 cases per 100,000 women of reproductive age, followed by Southeast Asia. African-American and Filipino women, for example, have a higher risk of developing these diseases. Additionally, higher incidence rates were observed among Māori, Indigenous Australian, American Indian, and Alaska Native populations. On the other hand, the risk of hypertensive diseases of pregnancy among Pacific Islander populations is still a subject of debate (Jiang *et al.*, 2022).

From the Rochester Epidemiology Project, it was identified that the rate of pre-eclampsia per pregnancy in women under 20 was significantly higher than in women aged 20-34, with 6.5 cases per 100 pregnancies (95% confidence interval: 4.8 to 8.6) compared to 3.0 cases per 100 pregnancies (95% confidence interval: 2.7 to 3.4). Additionally, the rate of gestational hypertension was higher in women aged 35 and older (Garovic et al., 2020).

New evidence indicates that women with postpartum eclampsia face a higher risk of severe maternal morbidity compared to those who develop the disease before delivery. This study, however, has limitations due to the use of administrative database data, but the authors highlighted an increased risk of severe complications associated with recent postpartum hypertension compared to women who presented hypertension during pregnancy (12.1% vs 6.9%; $P<0.01$) (Hauspurg; Jeyabalan, 2022).

According to data from recent studies, most women who present late-onset postpartum pre-eclampsia manifest symptoms in the first 7 to 10 days postpartum. The

most frequent symptoms are neurological, with headache being the most prevalent and the main reason for seeking medical assistance (Hauspurg; Jeyabalan, 2022).

In recent decades, there has been a substantial increase in the prevalence of hypertension, resulting in a greater number of cases of hypertensive emergencies and urgencies recorded in emergency departments (Vallelonga *et al.*, 2020). Recently, there has been a growing trend in recognizing hypertensive urgencies, which have a higher prevalence compared to hypertensive emergencies, possibly due to better patient education on the importance of blood pressure control and greater access to healthcare (Vallelonga *et al.*, 2020). In the last 10 years, the definition of pre-eclampsia has been expanded to include cases without proteinuria but with dysfunction in maternal or uteroplacental organs. This change, adopted by the International Society for the Study of Hypertension in Pregnancy and the American College of Obstetricians and Gynecologists, is influencing clinical management, increasing hospitalizations and inducing labor (Jiang *et al.*, 2022).

The risks of renal and cardiac diseases in women with a history of hypertensive diseases in pregnancy have been underestimated. The percentage of women at risk due to these histories (15.3%) is comparable to the proportions of cardiovascular risk from smoking (13.7%), hyperlipidemia (14.8%), and diabetes (12%) (Garovic *et al.*, 2020). The increase in mortality rates from coronary heart disease among women aged 35 to 54 and in patients with severe pre-eclampsia, who face the risk of cardiovascular death shortly after pregnancies, along with recent evidence of increased rates of hypertensive diseases of pregnancy over the last three decades, indicates the growing relevance of this specific risk factor for cardiovascular diseases (Garovic *et al.*, 2020).

Risk factors for hypertension in pregnancy include a history of previous gestational hypertension, family history of hypertension during pregnancy, and pre-existing medical conditions such as chronic hypertension, pre-gestational diabetes mellitus, thrombophilia, systemic lupus erythematosus, antiphospholipid antibody syndrome, kidney disease, and obstructive sleep apnea. Additionally, hypertensive and cardiometabolic diseases in pregnancy share risk factors such as advanced maternal age, overweight or obesity, inadequate nutrition, and dietary habits before and/or during pregnancy. A study revealed that women exposed to indoor air pollution, especially those using biomass and solid fuels, have twice the chance of reporting symptoms of pre-eclampsia compared to those using clean fuels (Jiang *et al.*, 2022).

Advanced maternal age, black race, and maternal obesity are associated with a higher risk of postpartum eclampsia. Women over 35 years of age have twice the risk of postpartum eclampsia, while pre-gestational obesity increases this risk in a dose-dependent manner, reaching 7.7 times for a BMI >40 kg/m². Black women have a 2 to 4 times higher risk of postpartum eclampsia compared to other races (Hauspurg; Jeyabalan, 2022). Younger patients tend to develop hypertensive urgencies more frequently than hypertensive emergencies, with an average age difference of 5.4 years (Vallelonga *et al.*, 2020). Women

with gestational hypertension have an increased risk of future cardiovascular events and other conditions such as arrhythmias, coronary artery disease, heart failure, stroke, chronic kidney disease, dementia, hyperlipidemia, hypertension, and diabetes, regardless of factors such as education, smoking, and obesity (Garovic *et al.*, 2020).

Currently, various approaches are used in clinical practice for the treatment and prevention of hypertensive diseases during pregnancy, including calcium, vitamin D, and folic acid supplementation, as well as the use of aspirin or antiplatelet agents (Jiang et al., 2022). Lifestyle interventions, such as education, diet, exercise, and personal monitoring of blood glucose levels, are also implemented. However, there is no conclusive evidence on the effectiveness of these interventions in preventing hypertensive diseases in pregnancy. A Cochrane review showed an average risk reduction of 0.70 (95% CI 0.40-1.22; four trials, 2,796 women; I2=79%; low-quality evidence) with these interventions (Jiang *et al.*, 2022).

To improve screening and treatment of gestational hypertensive diseases, it is essential that public health accurately assess how these disorders are coded in US birth records. Due to the low number of births in some locations or lack of reporting, it was not feasible to estimate the variation in the prevalence of each hypertensive disorder at the county level. Collecting accurate data from all counties can help public health authorities identify areas that need increased surveillance and treatment, especially in states with high prevalence of these disorders (Butwick; Druzin; Shaw and Guo, 2020).

It is recommended to consider the diagnosis of postpartum eclampsia in women who develop eclampsia between 48 hours and 6 weeks postpartum. For pre-delivery onset eclampsia, it is suggested that confirmation of elevated blood pressure be performed on two occasions separated by at least 4 hours, except in cases of severe hypertension, where confirmation should be immediate to allow for urgent treatment. Since there are no specific definitions for the postpartum period by the American College of Obstetricians and Gynecologists, it is proposed that the presence of any severe features (such as severely elevated blood pressure in women without a previous history of hypertension) be classified as postpartum eclampsia after excluding other possible causes (Hauspurg; Jeyabalan, 2022).

Including the history of hypertensive diseases in pregnancy can substantially reduce misclassification using current cardiovascular disease risk scores, which are particularly inaccurate in women. The proportion of women who may be at risk based on their history of hypertensive diseases in pregnancy is similar to the proportions of women at risk for cardiovascular diseases based on the presence of traditional risk factors (Garovic et al., 2020).

DIAGNOSIS

Early identification of the signs and symptoms of gestational hypertension and pre-eclampsia improves prognosis and prevents emergencies such as eclampsia or HELLP syndrome. It is essential to monitor pregnant women with hypertension associated with headache, visual disturbances, severe abdominal pain (especially in the upper right quadrant or epigastric), lower limb edema, and laboratory changes such as proteinuria, elevated transaminases, and thrombocytopenia. Any suspected pre-eclampsia or hypertensive emergency should be referred for hospital evaluation (Arbe; Pastor and Franco, 2018; Cífková, 2023).

In the assessment of hypertension in pregnancy, a systematic approach is essential, involving blood pressure measurement, laboratory tests, and umbilical artery Doppler ultrasound. Hypertension is diagnosed with SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, confirmed on two separate occasions or at intervals of at least 15 minutes for severe hypertension (≥ 160/110 mmHg). Laboratory tests are crucial to identify complications such as proteinuria (> 0.3 g/24h or > 30 mg/mmol in the protein/creatinine ratio), elevated serum creatinine (> 90 µmol/L) for acute kidney injury, and liver enzymes (alanine aminotransferase > 40 IU) to assess liver involvement. Platelet count and hemolysis detection help diagnose HELLP syndrome (thrombocytopenia < 150 × 10^9/L and hemolysis). Doppler ultrasound is used to assess uteroplacental insufficiency, associated with fetal growth restriction, depending on the operator's experience (Cífková, 2023; Sinkey *et al*., 2020; Wiles; Damodaram and Frise, 2021).

Each diagnostic method has its specificities, sensitivities, and limitations. Blood pressure measurement is simple and accessible but susceptible to technical and environmental variations. Proteinuria assessment is specific but can be influenced by inadequate samples or urinary infections. Creatinine and liver enzyme tests are sensitive to renal and hepatic lesions but do not adequately distinguish pre-eclampsia from other conditions. Doppler ultrasound, effective in detecting uteroplacental insufficiency, requires operational skill. Combining these methods allows for accurate diagnosis of hypertensive conditions in pregnancy, guiding clinical management and appropriate interventions (Cífková, 2023; Wiles; Damodaram and Frise, 2021; Sinkey *et al*., 2020).

In the differential diagnosis of hypertension in pregnancy, it is crucial to distinguish pre-eclampsia from other conditions with similar symptoms, such as gestational hypertension, renal diseases, and metabolic disorders. Pre-eclampsia manifests with hypertension and significant proteinuria, differing from gestational hypertension which occurs without proteinuria, and chronic hypertension which persists before and after pregnancy. Symptoms such as headache, visual disturbances, abdominal pain, and laboratory changes (low platelet count and abnormal liver enzymes) help distinguish pre-eclampsia. Associated conditions such as multiple pregnancy, hydatidiform mole, antiphospholipid syndrome, and

comorbidities like renal disease or diabetes influence clinical presentation. Differentiating these conditions is crucial for immediate interventions in pre-eclampsia and monitoring gestational hypertension to prevent complications (Arbe; Pastor and Franco, 2018; Wiles; Damodaram and Frise, 2021).

Recent advances include studies on serum total bile acid (TBA) as a biomarker associated with pre-eclampsia. The increased incidence of pre-eclampsia in patients with intrahepatic cholestasis suggests a significant relationship. Elevated TBA levels are correlated with the severity of pre-eclampsia, indicating its potential as a prognostic indicator and monitoring for recent-onset hypertension in pregnancy. It is recommended to include TBA tests in routine exams for pregnant women as a risk assessment for hypertensive disorders (Deng *et al.*, 2022).

TREATMENT

Treatment aims to reduce maternal and fetal morbidity and mortality, preventing complications such as prematurity, oligohydramnios, and fetal growth restriction (Vadhera; Simon, 2014). Despite challenges in developing new drugs, current treatments provide effective clinical management, reducing the risk of serious complications such as acute pulmonary edema, stroke, renal dysfunction, and mortality. The goal is to stabilize the patient, minimize damage to target organs, and ensure fetal viability (Cífková, 2023).

Initial treatment of gestational hypertension involves the use of antihypertensives, initiated when diastolic blood pressure (DBP) reaches values above 100-110 mmHg. Laboratory tests and ultrasound are complementary tools in patient management. Therapeutic adjustments are necessary based on response to treatment and blood pressure control. Clinical and laboratory manifestations should be monitored carefully, guiding adjustments and hospital interventions (Vadhera; Simon, 2014).

Pregnant women with hypertensive emergencies are at higher risk of developing acute pulmonary edema and stroke due to changes in hydrostatic pressure and uteroplacental flow. For severe hypertension (BP > 160/110 mmHg), with or without target organ involvement, intravenous medications such as labetalol, hydralazine, and nifedipine are indicated, with maternal intra-hospital monitoring. During stabilization, it is crucial to periodically monitor fetal heart rate to assess its viability, considering delivery as the definitive treatment after maternal stabilization in pregnancies beyond 34 weeks (Vadhera; Simon, 2014).

European guidelines recommend initiating medication in pregnant women with persistent elevation of blood pressure ≥ 150/95 mmHg, or values > 140/90 mmHg in cases of gestational hypertension (with or without proteinuria), chronic hypertension superimposed on gestational, or subclinical or symptomatic target organ damage, at any stage of pregnancy. Preferred drugs include methyldopa, labetalol, and calcium antagonists, with the most evidence of safety available for nifedipine (Cífková, 2023).

Women who develop postpartum pre-eclampsia (recent-onset hypertension, 48 hours to 6 weeks postpartum) should be treated when BP values reach 150/110 mmHg, to prevent progression to severe hypertension. Treatment includes the use of antihypertensives such as labetalol, intravenous hydralazine, and oral nifedipine. For women with severe hypertension and neurological symptoms postpartum, magnesium sulfate prophylaxis is recommended. Volume overload management is based on the use of diuretics, preferably IV or oral furosemide for 3 to 5 days, aiming to stimulate diuresis and reduce excess volume and BP (Hausurg; Jeyabalan, 2022).

Non-pharmacological interventions play a crucial role in preventing gestational complications such as hypertensive disorders and gestational diabetes mellitus. Obesity is a significant risk factor. For pregnant women with overweight (BMI 25.0-29.9 kg/m²), it is recommended to limit weight gain to 6.8-11.2 kg, while those with obesity (BMI ≥ 30 kg/m²) should restrict it to a maximum of 6.8 kg. These measures are essential to mitigate maternal-fetal risks. Regular physical activity during pregnancy is advisable to prevent the development of gestational diabetes and hypertensive disorders. Supervised aerobic exercises of light to moderate intensity, performed three to four times a week for 30 to 60 minutes, should be initiated in the first trimester, except in cases of contraindications (Cífková, 2023).

Table 1.0 - Prophylactic Medications for Pre-eclampsia and Eclampsia

Medications	Dose	Considerations
Aspirin PO	75 to 150 mg	Recommended for high-risk women between 12 and 28 weeks of gestation
Magnesium sulfate IV	Loading dose: 4g	Continuous infusion: 1g/h until delivery, for a maximum of 24h

Source: Cífková (2023).

Table 2.0 - Medications Used in Gestational Hypertensive Emergencies

Medications	Dose	Precautions	Considerations
Labetalol	100 to 800 mg	Asthma	Monitor neonatal hypoglycemia
Nifedipine	10 to 40 mg		
Methyldopa	250 mg - 1 g	Liver dysfunction	Mood disorder
Labetalol	Bolus: 10 to 50 mg infused over 1 to 2 min, every 10 min, with a maximum of 4 doses	Infusion: 20 mg/h, every 30 min, with a maximum of 160 mg/h	Asthma
Hydralaze	Bolus: 5 mg over 10 min, repeated every 20 to 30 min	Infusion: 5 mg/h	Maternal tachycardia

Source: Braunthal; Brateanu (2019); Sinkey *et al.* (2020); Tita *et al.* (2022); Vadhera; Simon (2014); Cífková (2023).

Home blood pressure monitoring (BP) is recommended for pregnant women with a history of hypertension, using antihypertensives, at high risk of pre-eclampsia, and those who develop hypertensive disorders during pregnancy. This practice is particularly useful for detecting BP elevations between the third and seventh day postpartum, facilitating early detection of severe hypertension and promoting appropriate management. However, evidence on its effectiveness in reducing outpatient visits and hospital interventions is still limited (Cífková, 2023).

Studies are being conducted to evaluate the withdrawal of hydralazine as a first-line drug in treatment due to its association with persistent arterial hypertension and complications such as maternal hypotension, cesarean section, premature placental abruption, oliguria, fetal cardiac arrhythmias, and low Apgar score in the first minute (Braunthal; Brateanu, 2019). In 2011, the World Health Organization (WHO) recommended the use of magnesium sulfate for prophylaxis, along with low-dose aspirin and calcium supplementation for areas with low intake. Interventions that have not demonstrated benefits, such as vitamin C, D, or E supplementation, bed rest, and sodium restriction, are discouraged. Diuretics and corticosteroids are contraindicated for complications. The International Federation of Gynecology and Obstetrics (FIGO) is evaluating the feasibility of additional ultrasound examinations, although the cost-benefit of this proposal needs further study (Sinkey *et al.*, 2020).

REFERENCES

ARBE, Guillermo; PASTOR, Irene; FRANCO, Jonathan. Diagnostic and therapeutic approach to the hypertensive crisis. **Medicina Clínica (English Edition)**, v. 150, n. 8, p. 317-322, 2018.

BRAUNTHAL, Stephanie; BRATEANU, Andrei. Hypertension in pregnancy: Pathophysiology and treatment. **SAGE open medicine**, v. 7, p. 2050312119843700, 2019.

BUTWICK, Alexander J.; DRUZIN, Maurice L.; SHAW, Gary M.; GUO, Nan. Evaluation of US state–level variation in hypertensive disorders of pregnancy. **JAMA network open**, v. 3, n. 10, p. e2018741-e2018741, 2020.

CÍFKOVÁ, Renata. Hypertension in pregnancy: a diagnostic and therapeutic overview. **High Blood Pressure & Cardiovascular Prevention**, v. 30, n. 4, p. 289-303, 2023.

DENG, Weinan et al. The association of serum total bile acid with new-onset hypertension during pregnancy. **BMC Pregnancy and Childbirth**, v. 22, n. 1, p. 879, 2022.

GAROVIC, Vesna D. et al. Incidence and long-term outcomes of hypertensive disorders of pregnancy. **Journal of the American College of Cardiology**, v. 75, n. 18, p. 2323-2334, 2020.

HAUSPURG, Alisse; JEYABALAN, Arun. Postpartum preeclampsia or eclampsia: defining its place and management among the hypertensive disorders of pregnancy. **American journal of obstetrics and gynecology**, v. 226, n. 2, p. S1211-S1221, 2022.

JIANG, Li et al. A global view of hypertensive disorders and diabetes mellitus during pregnancy. **Nature Reviews Endocrinology**, v. 18, n. 12, p. 760-775, 2022.

SINKEY, Rachel G. et al. Prevention, diagnosis, and management of hypertensive disorders of pregnancy: a comparison of international guidelines. **Current hypertension reports**, v. 22, p. 1-10, 2020.

VADHERA, Rakesh B.; SIMON, Michelle. Hypertensive emergencies in pregnancy. **Clinical Obstetrics and Gynecology**, v. 57, n. 4, p. 797-805, 2014.

WILES, Kate; DAMODARAM, Mellisa; FRISE, Charlotte. Severe hypertension in pregnancy. **Clinical Medicine**, v. 21, n. 5, p. e451, 2021.

WILKERSON, R. Gentry; OGUNBODEDE, Adeolu C. Hypertensive disorders of pregnancy. **Emergency Medicine Clinics**, v. 37, n. 2, p. 301-316, 2019.

Chapter 13

CARDIORESPIRATORY ARREST IN PREGNANT WOMEN

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CHAPTER 13

CARDIORESPIRATORY ARREST IN PREGNANT WOMEN

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Cardiorespiratory arrest (CRA) during pregnancy is a critical situation that demands immediate attention. The medical team must be familiar with the physiological changes of pregnancy and follow appropriate protocols. High-quality chest compressions and adequate oxygenation are essential. Manual displacement of the uterus to mitigate aortocaval compression should be performed promptly, and a

perimortem cesarean section may be indicated if the gestational age is greater than 20 weeks. An analysis of 462 cases of maternal CRA found that 41% of women survived to hospital discharge (Zelop *et al*., 2018).

Cardiovascular diseases (CVDs) complicate 1-2% of pregnancies and are a significant cause of morbidity and mortality. In developed countries, CVDs are the leading cause of maternal mortality due to increased maternal age, better survival of women with congenital heart diseases, and advances in assisted reproduction. Cardiac arrhythmias are a significant complication, influenced by pre-existing conditions and pregnancy-related changes (Muñoz-Ortiz *et al*., 2024).

The COVID-19 pandemic brought specific challenges for pregnant women, who are at higher risk of severe complications, including ICU admission and invasive ventilation. Risk factors include obesity, advanced maternal age, non-white ethnicity, pre-existing diabetes, and pre-eclampsia. Obstetric complications associated with CRA have been linked to such comorbidities, presenting numerous challenges (Allotey *et al*., 2020).

Twin pregnancies, representing 2-4% of births, vary in prevalence in Brazil due to socioeconomic disparities. Associated with higher risks of maternal and perinatal morbidity, this condition requires specialized care to prevent maternal and fetal harm, including CRA. Dizygotic twins are more prevalent and influenced by geographic and socioeconomic factors, while monozygotic twins have a genetic basis. Maternal mortality is 2.5 times higher, and perinatal mortality is two to three times higher in twin pregnancies (Santana; Surita and Cecatti, 2018).

EPIDEMIOLOGY

Cardiorespiratory arrest in pregnant women, characterized as one of the main causes of maternal morbidity and mortality, shows significant prevalence in emergency contexts. This condition poses a simultaneous risk to both mother and fetus, exacerbated by the physiological changes of pregnancy and specific obstetric causes requiring rapid decisions and specialized protocols. The incidence distribution of cardiorespiratory arrest in pregnant women is related to various pathophysiologies, including hemorrhages, cardiovascular abnormalities, and hypertensive disorders. Risk factors such as age, maternal comorbidities, and economic and social disparities also play an important role. These trends have direct implications for the organization of emergency services and the formulation of public strategies aimed at prevention and immediate care (Muñoz-Ortiz *et al*., 2024).

Cardiac arrest during pregnancy is a severe public and individual health situation, with the potential to lead to maternal and fetal death. Currently, it is recognized as a significant cause of maternal death worldwide, with cardiovascular diseases being a frequently involved factor (Muñoz-Ortiz *et al*., 2024). Historically, there has been an increase in the rates of cardiac arrest in pregnant women, attributed to increased maternal comorbidities, healthcare

failures, and rising socioeconomic, racial, ethnic, and demographic inequalities, as well as improved case records and descriptions. Despite this, evidence suggests a reduction in post-cardiac arrest mortality, especially in cases of reversible etiology, highlighting the importance of post-arrest care beyond immediate treatment (Zelop *et al.*, 2018).

Cardiovascular diseases are the leading cause of indirect maternal mortality, representing one-third of deaths in pregnant women (Alkema et al., 2016). White women have a 1.4 times higher rate of cases compared to black women (Zelop *et al.*, 2018). However, if managed early, almost 70% of maternal deaths can be prevented (Zaharatos *et al.*, 2018). Comparing underdeveloped and developed countries, the incidence of cardiac arrest in pregnant women is three times higher in the former (Ford *et al.*, 2023; Nivatpumin et al., 2021). Among obstetric risk factors, hemorrhages and gestational hypertension stand out as targets for management, prevention, and follow-up (Pawar *et al.*, 2023).

Studies conducted in the United States between 2017 and 2019 observed an average of one cardiac arrest per 9,000 deliveries, with a survival rate of 70% (Ford *et al.*, 2023). In contrast, another study found an incidence rate almost three times higher, with one cardiac arrest per 3,886 deliveries (Nivatpumin *et al.*, 2021). These data emphasize the influence of environmental and socioeconomic factors on maternal and fetal morbidity and mortality.

DIAGNOSIS

Rapid diagnosis is crucial to improve the prognosis of the pregnant woman and prevent severe cardiac complications such as CRA. Most cardiac complications occur in the third trimester of pregnancy. It is important to classify the causes according to the trimester of presentation: in the first trimester, atherosclerosis is the leading cause of acute myocardial infarction, especially in the presence of risk factors. In the second trimester, the main causes include atherosclerosis and thrombosis, while in the third trimester, spontaneous coronary artery dissection is the main cause (Pfaller *et al.*, 2020).

With continuous medical advances, many congenital heart diseases (CHDs) can be detected during pregnancy. However, some CHDs may still go unnoticed. The identification of serum biomarkers can complement routine cardiac ultrasound, reducing the prevalence and mortality of CHDs. Among these biomarkers, tRFs/tiRNAs have emerged as potential diagnostic and prognostic markers. These small RNAs derived from tRNA play essential roles in various cellular functions and are involved in pathological processes. The expression of tRFs/tiRNAs in the serum of pregnant women has been examined, and biological analysis concluded that these RNAs could be used as potential biomarkers for the detection of CHDs during pregnancy, offering a new approach to improving the treatment and prognosis of fetuses with CHDs (Lu *et al.*, 2023).

The diagnosis of peripartum cardiomyopathy (PPCM) is also discussed. Checking NT-proBNP levels, which do not vary significantly during pregnancy but are elevated in

PPCM, is essential for confirming the diagnosis. Other tests, such as electrocardiograms, may be normal or show nonspecific abnormalities. Echocardiography is fundamental for diagnosis, potentially revealing systolic dysfunction, left ventricular dilation, functional mitral and/or tricuspid regurgitation, right ventricular dysfunction, pulmonary hypertension, and atrial enlargement. If echocardiography is inconclusive, magnetic resonance imaging should be considered (Carlson; Schultz; Ramu and Davis, 2023).

TREATMENT

Effective treatment of CRA in pregnant women is crucial for maintaining the well-being of both mother and fetus. A rapid, effective, and multidisciplinary approach is essential to avoid unfavorable outcomes (Enomoto *et al.*, 2022). Protocols such as BLS, ACLS, and guidelines from the American Heart Association are fundamental. The first step is to declare the CRA state and activate the multidisciplinary team. Subsequent steps involve high-quality chest compressions, left uterine displacement, ventilation, intubation, defibrillation, use of vasoactive drugs, assessment of gestational age, and surgical interventions, with treatment scaled according to the patient's response (Zelop; Einav, Mhyre and Martin, 2018).

While the focus is on maternal-fetal well-being, resuscitation aims to restore maternal spontaneous circulation. Immediately after CRA is detected, the multidisciplinary team should start high-quality chest compressions on the lower third of the sternum, at a rate of 100 to 120 beats per minute, compressing about 5 to 6 cm. Every 30 compressions are followed by two ventilations with a bag-valve-mask device and 100% oxygen. Simultaneously, the uterus should be displaced to the left and two venous accesses established. Maternal oxygenation is a priority, and an advanced airway may be used to reduce compression-free intervals. Ventilations vary from 8 to 10 per minute. The rhythm should be analyzed, and if necessary, shocks applied with the same load as non-pregnant patients. Epinephrine is the vasoactive drug of choice, used every 3-5 minutes in non-shockable rhythms, while amiodarone is indicated for non-responsive shockable rhythms. Perimortem cesarean section should be considered within 4 minutes of the onset of CRA to improve fetal and maternal survival, especially from 20 weeks of gestation (Zelop; Einav; Mhyre and Martin, 2018).

Performing uterine displacement is essential to reduce pressure on the vena cava and increase blood return. However, this maneuver can be challenging as it requires an additional professional on the team (Maurin et al., 2019). Prehospital perimortem cesarean section can increase maternal survival chances but is limited by late arrival of emergency teams and lack of training among emergency physicians (Maurin *et al.*, 2019). Pregnant women with catecholaminergic polymorphic ventricular tachycardia (CPVT) should be monitored by cardiologists and obstetricians, with the use of safe antiarrhythmic medications and the programming of implantable cardioverter-defibrillators. Labor should be monitored according to risk, with atrioventricular nodal blockers and defibrillators available (Wong *et al.*, 2021).

The number of young women with ventricular cardiac arrhythmia using implanted cardiac devices (ICDs) is increasing, with about 3% of pregnant women being ICD carriers. The implantation of these devices can be safely performed during pregnancy but requires follow-up by a specialized multidisciplinary prenatal team (Wong et al., 2021). In the acute context of CRA, the drugs needed for resuscitation are used in the same doses as the general population, despite physiological changes during pregnancy (Zelop; Einav; Mhyre and Martin, 2018). In pregnant women with heart failure, the use of ivabradine should be carefully considered due to its potential fetal toxicity and teratogenicity (Karunarathna, 2024).

The compression generated by the gravid uterus can hinder maternal circulation, making it possible to perform manual uterine displacement to the left or lateralize the pregnant woman at 27 to 30 degrees to improve circulation. Intubations are more challenging during pregnancy due to airway narrowing by edema and fluid retention, requiring smaller endotracheal tubes (Zelop; Einav; Mhyre and Martin, 2018). These practices are essential to improve the effectiveness of cardiopulmonary resuscitation in pregnant women (Enomoto *et al.*, 2022).

REFERENCES

ALLOTEY, John et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. **bmj**, v. 370, 2020.

CARLSON, Selma; SCHULTZ, Jessica; RAMU, Bhavadharini; DAVIS, Melinda B. Peripartum cardiomyopathy: risks diagnosis and management. **Journal of Multidisciplinary Healthcare**, p. 1249-1258, 2023.

ENOMOTO, Naosuke et al. Effect of maternal positioning during cardiopulmonary resuscitation: a systematic review and meta-analyses. **BMC Pregnancy and Childbirth**, v. 22, n. 1, p. 159, 2022.

KARUNARATHNA, Indunil. Ivabradine Therapy in Heart Failure Management: Optimizing Outcomes Through Interprofessional Collaboration. **Uva Clinical Lab. Retrieved from Ivabradine Therapy in Heart Failure Management: Optimizing Outcomes Through Interprofessional Collaboration**, 2024.

LU, Enkang et al. Maternal serum tRNA-derived fragments (tRFs) as potential candidates for diagnosis of fetal congenital heart disease. **Journal of Cardiovascular Development and Disease**, v. 10, n. 2, p. 78, 2023.

MAURIN, Olga et al. Maternal out-of-hospital cardiac arrest: a retrospective observational study. **Resuscitation**, v. 135, p. 205-211, 2019.

MUÑOZ-ORTIZ, Edison et al. Characterization of cardiac arrhythmias and maternal–fetal outcomes in pregnant women: A prospective cohort study. **Revista Portuguesa de Cardiologia**, v. 43, n. 2, p. 67-74, 2024.

PFALLER, Birgit et al. Preventing complications in pregnant women with cardiac disease. **Journal of the American College of Cardiology**, v. 75, n. 12, p. 1443-1452, 2020.

SANTANA, Danielly Scaranello; SURITA, Fernanda Garanhani; CECATTI, José Guilherme. Multiple pregnancy: epidemiology and association with maternal and perinatal morbidity. **Revista Brasileira de Ginecologia e Obstetrícia**, v. 40, p. 554-562, 2018.

WONG, Geoffrey R. et al. Pregnancy in patients with implantable cardiac defibrillators. **Herzschrittmachertherapie+ Elektrophysiologie**, v. 32, n. 2, p. 214-220, 2021.

ZELOP, Carolyn M.; EINAV, Sharon; MHYRE, Jill M.; MARTIN, Stephanie. Cardiac arrest during pregnancy: ongoing clinical conundrum. **American journal of obstetrics and gynecology**, v. 219, n. 1, p. 52-61, 2018.

ZELOP, Carolyn M. et al. Characteristics and outcomes of maternal cardiac arrest: a descriptive analysis of Get with the guidelines data. **Resuscitation**, v. 132, p. 17-20, 2018.

Chapter 14

POSTPARTUM HEMORRHAGE

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CHAPTER 14

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Postpartum hemorrhage (PPH) is one of the leading causes of maternal mortality and morbidity worldwide. This condition occurs in approximately 1%-2% of deliveries and is responsible for around 150,000 deaths annually, representing 25% of global maternal deaths (Corvino *et al.*, 2021). PPH is characterized by blood loss exceeding 500 mL after vaginal delivery or 1000 mL after cesarean section, primarily

occurring within the first 24 hours postpartum (Watkins; Stem, 2020). Alternatively, any blood loss from the genital tract that compromises hemodynamic stability within this period also defines PPH. The causes of postpartum hemorrhage can be classified using the mnemonic of the 4 Ts: tone, trauma, tissue, and thrombin, with uterine atony being the most common cause, responsible for up to 80% of cases (Watkins; Stem, 2020). PPH can be classified as early postpartum hemorrhage, occurring within the first 24 hours after delivery, and late postpartum hemorrhage, occurring between 24 hours and 12 weeks postpartum. In terms of volume, massive PPH is defined by blood loss exceeding 2,000 mL in 24 hours, the need for a minimum transfusion of 1,200 mL, a hemoglobin drop of ≥ 4 g/dL, or the occurrence of coagulation disorders (Watkins; Stem, 2020). Given the potential risk, understanding the classification and manifestations of PPH is essential to ensure an effective management approach.

Postpartum hemorrhage stands out in the field of obstetric emergencies due to its high incidence and potential for severe complications. It demands rapid and effective interventions to prevent multi-organ failure and ensure maternal survival. Uterine atony, for example, is caused by the dysfunctional hypocontractility of the myometrium during the immediate postpartum period and is initially treated with measures such as uterine massage, uterotonics (oxytocin, carbetocin, methylergonovine maleate, prostaglandins), and administration of tranexamic acid (Li; Chang; Wang, 2022). However, it has been found that prolonged administration of oxytocin, especially for more than 4 hours in spontaneous deliveries and more than 7 hours in induced deliveries, is associated with a significant increase in the risk of PPH, regardless of the duration of hospitalization or the second stage of labor (Erickson; Carlson, 2020). The management of PPH involves a set of strategies, ranging from conventional medical treatments to advanced interventional procedures such as pelvic arterial embolization (Corvino *et al*., 2021). Even in the absence of robust evidence, international protocols agree on the main initial steps in the treatment of PPH, which include manual uterine exploration, visual evaluation of the genital tract, insertion of a bladder catheter, administration of supplemental oxygen, and infusion of crystalloids for maternal stabilization (Corvino *et al*., 2021). A multidisciplinary approach is fundamental for hemodynamic control and effective treatment of the underlying causes of hemorrhage (Erickson; Carlson, 2020). In this context, it is crucial to integrate different medical specialties to provide the best possible care for patients.

Postpartum hemorrhage (PPH) significantly affects maternal health globally, with incidences varying according to the definition and accuracy of blood loss measurement. Population studies indicate that the incidence of PPH can reach up to 10% when blood loss is precisely quantified. Risk factors include advanced maternal age, multiple pregnancies, and an increasing number of cesarean sections (Giurazza *et al*., 2021). PPH occurs in approximately 6% of all deliveries, with severe cases in 1%-2% (Corvino *et al*., 2021). Survivors of severe PPH often face physical and emotional sequelae, including sterility,

hormonal and organ dysfunctions, post-traumatic stress disorder, and depression (Brenner et al., 2023). Recent studies also suggest that women who do not receive oxytocin during labor (physiological delivery) may not benefit as much from prophylactic postpartum oxytocin in preventing PPH as those who received oxytocin during labor, indicating that previous exposure to oxytocin can influence the effectiveness of postpartum prophylaxis (Erickson; Carlson, 2020). These factors underscore the need for preventive interventions and long-term emotional support.

Early and accurate diagnosis of PPH is crucial for the implementation of immediate interventions. Traditional methods, such as clinical evaluation and measurement of blood loss, are complemented by emerging technologies, including the use of artificial intelligence for continuous monitoring and early diagnosis (Li; Chang and Wang, 2022). Imaging tools like ultrasound and computed tomography play a vital role in assessing the causes and determining appropriate treatment (Corvino *et al.*, 2021). Additionally, when hemorrhage persists after 15 to 30 minutes of initial treatment, the use of tranexamic acid, volume resuscitation, and intrauterine balloon tamponade are recommended before resorting to more invasive interventions such as surgery or radiological management. These strategies have been shown to reduce the need for procedures like pelvic arterial embolization (Corvino *et al.*, 2021). Technological advancements, therefore, play an increasingly important role in the early detection and personalized treatment of PPH.

Treatment options for PPH include aggressive fluid resuscitation, administration of uterotonic medications, and in severe cases, pelvic arterial embolization. The evolution of endovascular techniques offers an effective minimally invasive approach, preserving future fertility and reducing the need for hysterectomy (Brenner *et al.*, 2023). However, when conservative measures fail, surgical interventions such as arterial ligation and procedures like the B-Lynch suture may be necessary, although these techniques have variable success rates due to the complex pelvic vasculature (Corvino *et al.*, 2021). The use of nanotextile-based biosensors represents a new frontier in the sensitive diagnosis and targeted treatment of PPH (Watkins; Stem, 2020). With the adoption of these emerging technologies, the treatment of PPH is becoming increasingly effective and less invasive.

Current trends in managing PPH include the growing integration of advanced technologies such as artificial intelligence and nanotechnology to enhance early diagnosis and personalized treatment. The use of machine learning algorithms for continuous surveillance and identification of risk patterns promises to revolutionize the approach to PPH, improving maternal outcomes (Li; Chang and Wang, 2022). Additionally, the development of new therapeutic agents and strategies based on pharmacogenomics aims to combat drug resistance and optimize treatment efficacy (Erickson; Carlson, 2020). These innovations promise to transform the landscape of obstetric medicine in the coming years.

Prophylactic administration of uterotonics immediately after delivery significantly reduces the incidence of PPH. Oxytocin is frequently used, although its excessive use

can lead to complications (Li; Chang and Wang, 2022). However, the effectiveness of prophylactic oxytocin may be reduced in women who were not exposed to oxytocin during labor, highlighting the complexity of prophylactic management of PPH and the importance of individualizing therapeutic approaches. Early diagnosis of PPH is crucial and involves continuous monitoring of vital signs and precise estimation of blood loss (Erickson; Carlson, 2020). This preventive approach could be key to reducing the mortality and morbidity associated with PPH.

The initial management of postpartum hemorrhage (PPH) involves investigating the causes and implementing supportive measures, such as the insertion of a urinary catheter and the administration of supplemental oxygen. The use of crystalloids for volume resuscitation is preferred, and tranexamic acid has shown significant benefits when administered within the first three hours after the onset of hemorrhage (Giurazza *et al.*, 2021). The WOMAN study, which recruited more than 20,000 women with PPH, corroborated these findings by demonstrating that intravenous tranexamic acid reduces deaths from bleeding by about one-third when administered promptly (Brenner *et al.*, 2023). Additional measures include the use of sulprostone, intrauterine balloon tamponade, and, if necessary, surgical procedures such as B-Lynch suture and pelvic artery embolization (Brenner *et al.*, 2023). When conservative approaches fail to control the hemorrhage, surgical and radiological interventions, such as pelvic artery embolization (PAE) and vessel ligation, are recommended, despite limited evidence supporting their efficacy. PAE, for example, aims to reduce uterine blood flow to allow uterine involution to occur, but the rich vascularization of the female pelvis may limit the effectiveness of this technique (Corvino *et al.*, 2021).

In extreme situations where all conservative interventions fail, peripartum hysterectomy may be necessary as a last resort. This procedure is performed to ensure hemostasis and save the patient›s life, but it results in infertility and can be associated with substantial morbidity and psychosocial sequelae. The decision to perform a hysterectomy is complex and must consider all risks and benefits, as well as the long-term impact on the patient›s quality of life (Corvino *et al.*, 2021).

Thus, postpartum hemorrhage remains a significant challenge in obstetrics, requiring a multidisciplinary approach and the integration of new technologies to improve maternal outcomes. The prevention and early management of PPH, combined with individualized therapeutic interventions, are crucial to reducing the mortality and morbidity associated with this condition. As medical and technological innovations continue to evolve, it is expected that the management of PPH will become even more effective, providing better outcomes for women worldwide.

EPIDEMIOLOGY

Postpartum hemorrhage (PPH) occurs in approximately 6% of all deliveries, with severe cases accounting for 1%-2%. It is the leading cause of maternal mortality worldwide, responsible for about 25% of pregnancy-related deaths, totaling approximately 70,000 annual deaths (Neary *et al.*, 2021). The prevalence is higher in developing countries but is also increasing in developed countries. PPH predominantly affects women of reproductive age, with higher incidence among those with risk factors such as multiparity, previous cesarean sections, and multiple pregnancies (Feduniw *et al.*, 2020). In the United States, Black women have a threefold higher risk of dying from pregnancy complications compared to White women.

Historically, PPH has been a persistent concern in obstetrics. Recently, there has been an increase in the incidence of PPH in developed countries, possibly due to factors such as rising cesarean rates and advanced maternal age. Changes in obstetric practice and improvements in early diagnosis and treatment have also influenced these trends (Ashwal *et al.*, 2022).

Risk factors for PPH include uterine atony, which accounts for 70% of cases, followed by placental problems, trauma, and coagulopathies (Feduniw et al., 2020). Other risk factors include obesity, advanced maternal age, multiparity, prolonged or very rapid labor, and medical conditions such as maternal hypertension and prepartum anemia (Chainarong; Deevongkij and Petpichetchian, 2022).

The maternal mortality rate due to PPH is significant. It is estimated that PPH is responsible for about 25% of maternal deaths globally, with higher incidence in low- and middle-income countries. In the United States, the mortality rate is higher among Black women, reflecting racial and socioeconomic disparities in access to and quality of obstetric care (Borovac-Pinheiro *et al.*, 2021). Prevention and early diagnosis are crucial in reducing the morbidity associated with PPH. Prophylactic administration of uterotonics immediately after delivery reduces the incidence of PPH by 50% and severe PPH by 40% (Omotayo *et al.*, 2021). Diagnosis is based on clinical evaluation, with visual estimation of blood loss and weighing blood-soaked products being common methods, though often imprecise.

Protocols for managing PPH include medical interventions, intravenous fluid and blood product resuscitation, the use of uterotonic medications, and surgical options. Uterine artery embolization stands out as a minimally invasive treatment that preserves the uterus. In more severe cases, hysterectomy may be necessary, though it is associated with high morbidity and psychosocial sequelae (Franke *et al.*, 2021). PPH represents a significant challenge in modern obstetrics. Effective prevention, early diagnosis, and appropriate management are essential for improving maternal outcomes and reducing the mortality associated with this critical condition (Liu *et al.*, 2021).

DIAGNOSIS

The diagnosis of postpartum hemorrhage (PPH) is a daily challenge faced by obstetric care worldwide. This condition is often undetected or detected late, compromising prognosis and maternal health. Severe maternal hemodynamic changes can be avoided with early diagnosis and rapid treatment, accelerating the return to health, preventing further consequences, and reducing maternal morbidity and mortality rates (Ruiz *et al.*, 2023; Gallos *et al.*, 2023). Effective measurement of blood loss, performed in various ways, is crucial to avoid a late diagnosis but also poses one of the biggest challenges in correctly diagnosing PPH, as blood loss is often underestimated. It is most commonly performed through visual estimation, weighing of surgical sponges and drapes, the use of graduated collectors along with clinical criteria and shock index, and recent diagnostic advances such as the use of artificial intelligence systems with colorimetry (Ruiz *et al.*, 2023; Gallos *et al.*, 2023).

PPH is characterized by significant blood loss following delivery, specifically defined as blood loss exceeding 1,000 mL accompanied by signs of hypovolemia within the first 24 hours postpartum. During a cesarean section, it is crucial to accurately quantify blood loss and continuously monitor the woman's hemodynamic status to prevent PPH. Distinguishing between blood and amniotic fluid is essential, usually performed using separate suction containers or measuring amniotic fluid prior to collection.

Strict monitoring of vital signs (heart rate, blood pressure) and the shock index is essential for diagnosing PPH. The physiological response to hemorrhage plays a crucial role in the early identification of high-risk cases. Measurement of hemoglobin (Hb) and/or hematocrit (Ht) before and after delivery is highly accurate for assessing blood loss. Healthcare teams trained in postpartum blood loss quantification methods show more robust results. Current methods use prenatal data, such as medical history and risk factors, to predict severe PPH. Ultrasound and magnetic resonance imaging (MRI) can be used to evaluate conditions such as placenta previa and uterine anomalies, effectively excluding certain factors (Pingray *et al.*, 2024; Alvez *et al.*, 2020; Lu *et al.*, 2024).

To effectively evaluate and manage postpartum hemorrhage, frequent monitoring of women's hemodynamic status is crucial, ideally every 15 minutes during the first 2 hours postpartum, and observation of clinical signs of internal bleeding, such as assessment of uterine fundal height. It is vital to evaluate postpartum vaginal blood loss using quantitative methods or estimates such as counting and weighing surgical sponges. In cases of suspected internal hemorrhage, urgent ultrasound is recommended for early diagnosis. The Obstetric Shock Index (OSI), calculated by dividing heart rate by systolic blood pressure, can be used as a clinical decision support tool. Prenatal platelet count has proven useful in predicting severe PPH, with low levels associated with a higher risk of complication. Various methods are used to estimate blood loss, including visual assessment, weighing surgical sponges, using calibrated collection devices, and comparing hemoglobin (Hb) and/

or hematocrit (Ht) levels. The application of technologies such as colorimetry using digital devices can enhance the accuracy of blood loss quantification.

Pregnant women with a history of previous cesarean sections should undergo ultrasound to locate the placenta, especially in cases of placenta previa or suspected placenta accreta, indicating the need for delivery in a tertiary care setting due to the high risk of PPH. These strategies aim to improve early diagnosis and appropriate management of PPH, reducing complications and improving outcomes for patients (de Moreuil *et al.*, 2023; Ruiz *et al.*, 2023).

Various gestational conditions can lead to postpartum hemorrhage (PPH) and consequently make it difficult to distinguish symptoms in their early stages. Uterine atony, placenta accreta, lacerations of the birth canal, placental disorders, and coagulopathy are examples of conditions that, like PPH, present with heavy vaginal bleeding, low heart rate, sweating, dizziness, and altered consciousness. In these cases, a comprehensive ultrasound evaluation, physical examination, and vital signs assessment are necessary to accurately detect the etiology of the bleeding, ensure the correct diagnosis, and provide specific treatment for each situation (Pingray *et al.*, 2024; Alvez *et al.*, 2020; Lu *et al.*, 2024).

With the established consensus on a single definition, independent of the specific characteristics of each delivery, new protocols are being implemented, from early detection to treatment. Regarding the initial response phase, an individualized approach is expected, evaluating blood loss through quantitative measurements (counting and weighing), complemented by monitoring the woman's hemodynamic status (ideally every 15 minutes during the first 2 hours) and clinical signs (assessing the height of the uterine fundus). In addition, quantitative measurement and monitoring should be incorporated into routine practice, along with strategies to prevent PPH. It is also crucial to consider coagulopathy as a possible cause of hemorrhage, requiring specific guidelines on the appropriate blood products for the woman's context (Pingray *et al.*, 2024).

Regarding biomarkers linked to severe postpartum hemorrhage, platelet count was the only one significantly associated. It was observed to be low in women in the prepartum phase, and consequently, those who had severe PPH in the postpartum phase. This mechanism is explained by the formation of clots and hemorrhage control conducted by platelets (de Moreuil *et al.*, 2023).

Analysis of the teams present at delivery shows that the better trained the care team is in postpartum blood loss quantification methods, the fewer discrepancies and more reliable the quantifications will be. This leads to early diagnosis, determination of the cause of the hemorrhage, and the best course of action for each case, reducing maternal mortality rates due to postpartum hemorrhage (Ruiz *et al.*, 2023).

TREATMENT

In the occurrence of abnormal postpartum uterine bleeding, conservative treatment is initially performed. To reduce bleeding, the Hamilton maneuver is performed on anesthetized patients or those with higher tolerance to bimanual uterine compression, or the Chantrapitak maneuver is used. Continuous monitoring of the patient is essential for calculating the shock index, and two large-bore intravenous accesses are established for the infusion of crystalloids, medications, and blood tests (blood typing, crossmatching, complete blood count, coagulation profile, fibrinogen, electrolytes, clot test, and in severe cases, lactate analysis and blood gas analysis). Oxygenation with a face mask (100% O2 at a flow rate of 8 to 10 liters per minute) and permanent urinary catheterization should also be instituted. Additionally, measures such as elevating the lower limbs, warming the patient, evaluating antibiotic prophylaxis, estimating blood loss, and quickly assessing the etiology with localization of the hemorrhage focus are employed according to the cause of the hemorrhage (Alvez *et al*., 2020; Hofer *et al*., 2023).

Uterine massage is a technique used to stimulate uterine contraction and reduce blood loss. To perform bimanual uterine compression, either the Hamilton or Chantrapitak maneuver can be used (Lu *et al*., 2024). Another mechanical therapy is the use of an intrauterine balloon for tamponade. Its primary indication is when medications do not adequately control the hemorrhage or cannot be administered due to contraindications. These devices apply pressure to the vasculature by expanding against the internal walls of the uterus for 12 to 24 hours. Contraindications include pregnancy, internal genital infections, abnormalities that distort the uterine cavity, uterine rupture, allergy to balloon components, and arterial bleeding requiring surgical treatment or embolization (D'Alton *et al*., 2021; Alvez*et al*., 2020).

Additionally, the NASG (Non-Pneumatic Anti-Shock Garment) is a segmented neoprene garment that covers the lower limbs and abdomen from the ankle to the last rib, applying external compression. It is a low-cost, easy-to-use device that aids in volume resuscitation and the treatment of severe forms of PPH (Alvez *et al*., 2020).

Tranexamic acid (TXA) is an antifibrinolytic medication that reduces bleeding by inhibiting the interaction of plasminogen with fibrin, thereby reducing plasmin activation and consequently clot breakdown. The WOMAN study demonstrated that early administration within 3 hours after birth reduces PPH-related deaths and the need for surgical intervention to control hemorrhage without increasing the risk of vascular occlusive events (McLintock, 2020). This placebo-controlled clinical trial conducted in 21 countries analyzed the impact of TXA on 20,021 women with PPH > 500 mL after vaginal delivery or > 1,000 mL after cesarean section. The World Health Organization (WHO) recommends the intravenous administration of 1g of TXA diluted in 100mL of 0.9% saline solution. If bleeding continues after 30 minutes or restarts within 24 hours, a second intravenous dose of 1g is recommended (Roberts; Brenner and Shakur-Still, 2023; D'Alton *et al*., 2020).

Uterotonics and tranexamic acid should be the first medications administered. As a first choice, oxytocin should be infused slowly (5 units over three minutes), followed by 20 to 40 units in 500 mL of saline solution infused at 250 mL/hour. A maintenance dose of 125 mL/hour for 4 hours should be administered. In more severe cases of uterine atony, this maintenance can be considered for up to 24 hours (67.5 mL/hour or 3 units/hour) with monitoring for water intoxication (Alvez *et al*., 2020).

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If there is no response to oxytocin and if there is no hypertension or use of protease inhibitors, the second-choice medication is methylergonovine at a dose of 0.2 mg intramuscularly, which can be repeated after 20 minutes. The third and final option for uterotonic medication is prostaglandin, with rectal administration of 800 to 1,000 mcg of misoprostol or sublingual administration of 600 mcg (Alvez *et al*., 2020).

Blood component transfusion is essential for patients with significant blood loss. Early consideration of coagulopathy treatment is crucial, especially in etiologies with a higher risk of coagulopathy, such as abruptio placentae. The use of red blood cells, fresh frozen plasma, and platelets in women with PPH > 1,500 mL has been shown to be effective in reducing progression to severe PPH (McLintock, 2020).

Common hemostatic methods include tamponade of the uterine cavity, uterine compression sutures, uterine artery ligation, and blood volume supplementation. Uterine compression sutures are widely used in obstetrics to achieve hemostasis by compressing the uterus with sutures. However, there is still room for improvement due to the complexity of the procedure, long recovery time, and increased risk of infection following maternal exposure (Liu *et al*., 2024).

A vacuum intrauterine device, known as the Jada System, uses low-level vacuum to induce uterine myometrial contraction and control postpartum uterine bleeding. This device is designed to offer rapid and effective treatment of hemorrhage, being applied for at least 1 hour. A multicenter prospective study conducted in 12 centers in the United States evaluated the effectiveness of this device, observing a success rate in treatment in 96% of participants (D'Alton *et al*., 2020).

Another device studied to control PPH is the Bakri Balloon, which can mechanically compress the uterine wound and promote local coagulation. Among various conservative procedures, the Bakri Balloon has notable advantages, such as minimal local requirements, little training needed, and high efficacy in maintaining fertility. A retrospective study conducted in China demonstrates that precise and timely intervention in the placement of the Bakri Balloon was crucial to control PPH in cesarean deliveries, especially in women with placenta accreta (Chen *et al*., 2023).

Treating pathological conditions related to uterine hemorrhage, especially PPH, presents several significant challenges. One of the main obstacles is the early and accurate diagnosis of the underlying cause of the hemorrhage. It is essential to quickly identify whether the cause is due to uterine atony, cervical trauma, retained products of conception, or another etiology to initiate appropriate treatment as soon as possible. Administering medications such as uterotonics and using established protocols are crucial steps in the first line of treatment. However, when these measures fail, prompt referral to a specialized tertiary center is necessary. In these centers, trained teams are prepared to intervene with more advanced techniques, such as using an intrauterine balloon for tamponade or aspiration systems. The additional challenge lies in the need for rapid and effective intervention, especially due to the potential hypovolemic shock that can occur quickly in severe cases of PPH. Coordination among healthcare professionals, the availability of adequate resources, and the knowledge to apply these techniques effectively are fundamental to ensuring the best possible health outcomes (Gallos *et al*., 2023; Alvez*et al*., 2020; Brenner *et al*., 2023).

REFERENCES

ASHWAL, Eran, *et al*. Risk factors for postpartum hemorrhage following cesarean delivery. **The Journal of Maternal-Fetal & Neonatal Medicine**, v. 35, n. 18, p. 3626-3630, 2022.

BOROVAC-PINHEIRO, Anderson; PRIYADARSHANI, Preeti; BURKE, Thomas F. A review of postpartum hemorrhage in low-income countries and implications for strengthening health systems. **International Journal of Gynecology & Obstetrics**, v. 154, n. 3, p. 393-399, 2021.

BRENNER, Amy, *et al.* Tranexamic acid by the intramuscular or intravenous route for the prevention of postpartum haemorrhage in women at increased risk: a randomised placebo-controlled trial (I'M WOMAN). **Trials**, v. 24, n. 1, p. 782, 2023.

CHAINARONG, Natthicha; DEEVONGKIJ, Kittiya; PETPICHETCHIAN, Chusana. Secondary postpartum hemorrhage: Incidence, etiologies, and clinical courses in the setting of a high cesarean delivery rate. **Plos one**, v. 17, n. 3, p. e0264583, 2022.

CORVINO, Fabio, *et al*. Postpartum hemorrhage: rescue. In: Seminars in Ultrasound, CT and MRI. **WB Saunders**, p. 75-84, 2021.

D'ALTON, Mary E., *et al.* Intrauterine vacuum-induced hemorrhage-control device for rapid treatment of postpartum hemorrhage. **Obstetrics & Gynecology**, v. 136, n. 5, p. 882-891, 2020.

D'ALTON, Mary, *et al*. Profile of the Jada® System: the vacuum-induced hemorrhage control device for treating abnormal postpartum uterine bleeding and postpartum hemorrhage. **Expert Review of Medical Devices**, v. 18, n. 9, p. 849-853, 2021.

DE MOREUIL, Claire, *et al.* Hemostatic biomarkers associated with postpartum hemorrhage: a systematic review and meta-analysis. **Blood Advances**, v. 7, n. 19, p. 5954-5967, 2023.

ERICKSON, Elise N.; CARLSON, Nicole S. Predicting postpartum hemorrhage after low-risk vaginal birth by labor characteristics and oxytocin administration. **Journal of Obstetric, Gynecologic & Neonatal Nursing**, v. 49, n. 6, p. 549-563, 2020.

FEDUNIW, Stepan, *et al*. Epidemiology, prevention and management of early postpartum hemorrhage—a systematic review. **Ginekologia polska**, v. 91, n. 1, p. 38-44, 2020.

FRANKE, Denise, *et al*. Retained placenta and postpartum hemorrhage: time is not everything. **Archives of Gynecology and Obstetrics**, v. 304, p. 903-911, 2021.

GALLOS, Ioannis, *et al.* Randomized trial of early detection and treatment of postpartum hemorrhage. **New England Journal of Medicine**, v. 389, n. 1, p. 11-21, 2023.

GIURAZZA, Francesco, *et al.* Postpartum hemorrhages: prevention. Seminars in Ultrasound, CT and MRI. **WB Saunders**, p. 85-94, 2021.

HOFER, Stefan, *et al*. Haemostatic support in postpartum haemorrhage: A review of the literature and expert opinion. **European Journal of Anaesthesiologyl EJA**, v. 40, n. 1, p. 29-38, 2023.

LI, Y.-T; CHANG, W.-H; WANG, P.-H. Postpartum hemorrhage. **Taiwanese Journal of Obstetrics & Gynecology**, v.61, p.5-7, 2022.

LIU, Chen-ning, *et al.* Prevalence and risk factors of severe postpartum hemorrhage: a retrospective cohort study. **BMC pregnancy and childbirth**, v. 21, n. 1, p. 332, 2021.

LU, Xian, *et al*. The value of the combined MR imaging features and clinical factors Nomogram model in predicting intractable postpartum hemorrhage due to placenta accreta. **Medicine**, v. 103, n. 13, p. e37665, 2024.

MCLINTOCK, Claire. Prevention and treatment of postpartum hemorrhage: focus on hematological aspects of management. **Hematology 2014, the American Society of Hematology Education Program Book**, v. 2020, n. 1, p. 542-546, 2020.

NEARY, Charlotte, *et al.* Predicting risk of postpartum haemorrhage: a systematic review. **BJOG: An International Journal of Obstetrics & Gynaecology**, v. 128, n. 1, p. 46-53, 2021.

OMOTAYO, Moshood O., *et al*. Prenatal anemia and postpartum hemorrhage risk: A systematic review and meta-analysis. **Journal of Obstetrics and Gynaecology Research**, v. 47, n. 8, p. 2565-2576, 2021.

PINGRAY, Verónica, *et al.* Strategies for optimising early detection and obstetric first response management of postpartum haemorrhage at caesarean birth: a modified Delphi-based international expert consensus. **BMJ open,** v. 14, n. 5, p. e079713, 2024.

ROBERTS, Ian; BRENNER, Amy; SHAKUR-STILL, Haleema. Tranexamic acid for bleeding: Much more than a treatment for postpartum hemorrhage. **American Journal of Obstetrics & Gynecology MFM**, v. 5, n. 2, p. 100722, 2023.

RUIZ, Mariana Torreglosa, *et al*. Quantification of blood loss for the diagnosis of postpartum hemorrhage: a systematic review and meta-analysis. **Revista Brasileira de Enfermagem**, v. 76, 2023.

WATKINS, Elyse J.; STEM, Kelley. Postpartum hemorrhage. **Jaapa**, v. 33, n. 4, p. 29-33, 2020.

Chapter 15

OBSTRUCTION OF AIRWAY BY FOREIGN BODIES IN PEDIATRICS

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CHAPTER 15

OBSTRUCTION OF AIRWAY BY FOREIGN BODIES IN PEDIATRICS

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A foreign body is any object or substance that penetrates the body or its cavities. Accidents involving foreign bodies are extremely common in children, especially in the age range of 0 to 3 years, which can result in drastic consequences and represent a public health problem. The

type of foreign body varies according to anatomical location, cultural habits, socioeconomic characteristics, and the intellectual level of the patient. Therefore, quick attention, accompanied by precise diagnosis and removal of the foreign body, is crucial to determine the patient's outcome and reduce associated morbidity and mortality (Bohadana; Santos; Magalhães and Cesar, 2023).

Foreign body aspiration is a frequently encountered situation in pediatric emergencies, where total or partial obstruction of the respiratory tract can hinder or even prevent air exchange between the lungs and the external environment. This can result in clinical events such as pneumonia, bronchiectasis, lung abscess, atelectasis, or even death. Unfortunately, accidents with foreign bodies are the leading cause of accidental death during the first year of life and the fifth cause of death among children aged one to four years. The severity of this emergency underscores the need for early intervention to avoid complications (Fasseeh *et al.*, 2021).

The incidence of foreign body aspiration is especially high in children under three years of age, with a higher prevalence in boys (Salih; Alfaki and Alam-Elhuda, 2016). Patients involved in this clinical emergency range from 0 to 15 years old (Bohadana; Santos; Magalhães and Cesar, 2023), with the ingestion of foreign bodies being the main cause of accidental death in the first year of life and the fifth cause among one to four years (Fasseeh *et al.*, 2021). In addition to age and gender, the type of foreign body, its location, and the time of ingestion are determining factors for potential complications (Oliva *et al.*, 2020). Due to the severity of these conditions, there is a trend not only to ensure effective prevention but also to enhance multidisciplinary emergency care (Bohadana; Santos; Magalhães and Cesar, 2023).

The diagnosis of foreign bodies in the respiratory system is crucial for the proper management of material removal and prevention of complications. A thorough clinical history and physical examination, along with complementary tests such as chest radiography, are essential. In these cases, diagnostic bronchoscopy is fundamental (Salih; Alfaki and Alam-Elhuda, 2016). Innovations such as the development of algorithms that increase diagnostic sensitivity and accuracy, including factors like witnessed choking, chest wheezing, and unilateral hyperinflation, have been successfully applied (Fasseeh *et al.*, 2021).

The treatment of foreign body ingestion in pediatric patients aims to remove the objects, following guidelines that optimize care in urgent and emergency situations. Emergency endoscopies are frequently used, with priority given to cardiopulmonary resuscitation in cases of clinical instability. In stable cases, other managements are suggested (Oliva *et al.*, 2020). Innovations in management include algorithms for correct bronchoscopic intervention. In recent years, significant advances in diagnostic and treatment techniques have been achieved. Rigid bronchoscopy remains the standard method for foreign body removal, while the growing use of flexible bronchoscopes offers a less invasive approach. Low-dose computed tomography has also improved the accuracy in identifying aspirated objects (Fasseeh *et al.*, 2021).

For prevention, it is essential that parents and caregivers closely supervise children, ensuring a safe environment, especially regarding toys and objects. The appropriate use of diagnostic techniques and treatment modalities, according to the type of foreign body, has proven highly effective, highlighting the importance of standardized protocols and specialized training for healthcare professionals in managing this condition (Salih; Alfaki and Alam-Elhuda, 2016).

EPIDEMIOLOGY

Understanding the epidemiology of foreign body aspiration in pediatric patients is essential for adequately planning healthcare processes and targeting population-specific care. Knowledge of prevalence, incidence, demographics, and geographic distribution of this condition is fundamental. Airway obstruction by foreign bodies is one of the leading causes of accidental deaths in children under five years old, with a particularly high incidence in children under three years, representing about 80% of cases (Salih, Alfaki and Alam-Elhuda, 2016). Children aged 0 to 2 years are especially vulnerable due to the still incomplete development of swallowing function, lack of teeth which hinders chewing, the habit of exploring objects with their mouths, and the practice of playing and moving while eating (Ding *et al.*, 2020).

Most foreign bodies obstructing the airways are organic in nature and often ingested by boys. However, cultural and geographical conditions of population groups influence the nature of these foreign bodies, mainly due to specific dietary habits of populations. While several studies indicate a higher prevalence in boys, some research shows similar incidence between genders, especially in younger age groups. Financial conditions and income of the population also affect the nature of ingested foreign bodies (Ding *et al.*, 2020). The ingestion of toxic substances and metallic objects is common among young children, especially boys under two years old. Coins are one of the most frequently ingested foreign bodies worldwide by children, and substances such as caustic soda and household cleaning products are often observed in pediatric emergencies. Children with psychiatric disorders and emotional disturbances are classified as a high-risk group for this condition (Speidel; Wölfle; Mayer and Posovszky, 2020).

Historically, cases of airway obstruction by aspiration of objects or food are very common and have been described numerous times over time. With the evolution of medicine and technological advances, the prognosis and survival rate of these cases have significantly improved. A notable example is the case of 1897, where Gustav Killian successfully managed the aspiration of a foreign body using bronchoscopy, becoming a pioneer in the extraction of these objects (Salih; Alfaki and Alam-Elhuda, 2016).

In the pediatric field, accidents related to foreign body aspiration are even more frequent compared to adults. This is due to several factors related to the physical

characteristics and physiological development milestones of children. The study by Speidel *et al*. (2020) analyzed 1,199 cases of pediatric accidents by foreign body aspiration and ingestion of chemical substances over 13 years (2005-2017) in a German University Medical Center, revealing a significant annual increase of 80%, from 6.1 in 2005 to approximately 11 per 10,000 children in 2017 in the coverage area. Additionally, the study by Ding *et al.* demonstrated that the incidence of foreign body aspiration cases was estimated at 29.9 per 100,000 pediatric inhabitants, accounting for 160 deaths in the USA in 2000.

Despite the increase in the number of cases over the years, there has not been a proportional increase in mortality. On the contrary, mortality rates have substantially decreased in the current context. This reduction in mortality can be attributed to significant advances in the medical field, especially regarding modern bronchoscopy techniques (Ding *et al.*, 2020).

Foreign body aspiration (FBA) presents a variety of risk factors, varying according to the type of inhaled object and the cultural and socioeconomic conditions of each region. In high- and middle-income countries, nuts are responsible for 40% of aspiration cases (Ding *et al.*, 2020). Besides the risk of choking on nuts, it is important to alert caregivers to the danger posed by small toys (Parvar *et al.,* 2023). The type of inhaled foreign body varies globally, reflecting differences in dietary habits of each country.

As discussed in the article "Airway Foreign Bodies: A Critical Review for a Common Pediatric Emergency," 91% of Western patients inhaled organic materials, with peanuts accounting for half of these cases, or 45.5%. On the other hand, bones were the most common foreign bodies in Southeast Asia and China. Watermelon seeds, sunflower seeds, and pumpkin seeds are more prevalent in Egypt, Turkey, and Greece, respectively (Salih; Alfaki and Alam-Elhuda, 2016).

The accidental ingestion of caustic substances is frequently reported in children worldwide, affecting up to 75% of children under six years old (Speidel; Wölfle; Mayer and Posovszky, 2020). Various objects and toxic substances are ingested by children, including coins, fish bones, toys, jewelry, button batteries, magnets, household utensils, cleaning products, and caustic soda (Speidel; Wölfle; Mayer and Posovszky, 2020).

FBA is a common problem in the pediatric emergency room, accounting for 2,000 hospitalizations and 17,500 emergency department referrals in the United States. It is the leading cause of distress, morbidity, and accidental infant deaths, as well as the fourth most prevalent cause of death in elementary school children (Parvar *et al.*, 2022).

A study conducted by Ding *et al.* (2020) on the prevalence of the type of aspirated object revealed that 93.3% of aspirated foreign bodies by children are organic in nature, with the vast majority being food items. Among these, 43.3% were peanuts, followed by watermelon seeds (13.9%) and sunflower seeds (9.8%).

Analyses of studies indicate that boys are the majority of foreign body aspiration cases in pediatrics (Salih; Alfaki and Alam-Elhuda, 2016). This can be explained by different

upbringing patterns between boys and girls, a higher level of motor activity among boys, and specific cultural and dietary variations between countries. This higher incidence in boys was identified mainly in Asian countries (Parvar *et al.*, 2022).

The prevalence of FBA is significantly higher in children under two years old, with more than three-quarters of cases occurring in this age group (Parvar *et al.*, 2022). Babies and young children are more likely to put objects in their mouths as a form of exploration, increasing the likelihood of swallowing them. This behavior is part of the child's natural development and, combined with the absence of premolars and molars and an immature gag reflex, results in a higher frequency of foreign body aspiration cases in children under three years old.

The complication rate is directly related to the time elapsed between aspiration and diagnosis/treatment. Many patients are referred to emergency rooms within the first 12 to 24 hours after aspiration. However, delays in diagnosis and hospital admission can result in long-term lung damage and complications such as air trapping, pneumonia, and atelectasis (Parvar *et al.*, 2022). After removing the foreign body, it is crucial that the main right and left bronchi and their respective branches are carefully investigated by bronchoscopy to detect any remaining objects or particles.

The socioeconomic status of the countries analyzed in the studies was a determinant for the prognosis of each case. In developing countries with middle-low income, there was a high incidence of complications, especially due to delays in diagnosis (Salih, Alfaki & Alam-Elhuda, 2016). This delay was attributed to the lack of experience of parents and doctors, the lack of bronchoscopy equipment, and the distance from major hospitals (Parvar *et al.*, 2022).

DIAGNOSIS

The diagnosis of foreign body aspiration in pediatrics involves the use of clinical history, physical examination, chest radiography, and rigid and flexible bronchoscopy. Common symptoms of obstruction include dry or wet cough, choking, dyspnea, wheezing, crackles, tachypnea, and fever, usually observed early within a week (Goyal *et al.*, 2020). On chest radiography, unilateral lung hyperinflation, collapse, consolidation, and mediastinal shift can be found, although in the early phase the radiograph may be normal (Truong and Luu, 2023).

Rigid bronchoscopy, considered the gold standard, is an invasive procedure under general anesthesia, crucial for early diagnosis and endoscopic removal to prevent complications such as lung collapse, pneumonia, and even death. Both rigid and flexible bronchoscopies present respiratory complications, such as desaturation and laryngospasm, with flexible bronchoscopy being preferred for its greater availability and safety (Wiemers *et al.*, 2023).

To determine the appropriate timing for endoscopy in children with ingested foreign bodies, factors such as age, body weight, clinical presentation, time since the last meal and ingestion, type, size, shape, and current location of the foreign body in the gastrointestinal tract are considered (Lee, 2018). Depending on the location of the foreign body, symptoms vary and determine the urgency of removal: in the esophagus, suspicion should be high in children with symptoms like sore throat or difficulty swallowing, with urgent removal in cases such as coins or sharp objects. In the stomach, button batteries should be removed quickly due to the risk of complications, while in the small intestine most foreign bodies pass spontaneously, with guidance for monitoring and seeking assistance if necessary (Lee, 2018).

The diagnosis of bronchial foreign body (BFB) is based on the typical history of aspiration, physical examination, and chest computed tomography, with the presence of choking witnesses being crucial for correct diagnosis. Even in the absence of a clear choking history, children with persistent respiratory symptoms should be investigated, as late diagnosis can lead to severe complications such as pneumonia and atelectasis (Wu *et al.*, 2019).

To differentiate the causes of pediatric nasal obstruction, it is essential to perform a detailed history and focused physical examination. Common causes include allergic rhinitis, characterized by symptoms like sneezing and rhinorrhea, and hypertrophy of adenoids and inferior turbinates, associated with sleep respiratory disorders and recurrent otitis. The insertion of nasal foreign bodies should also be considered, especially in cases of persistent unilateral discharge. The complete physical examination includes anterior rhinoscopy and otoscopy to evaluate the upper and middle airways, with referral to specialists for cases with warning signs (Sapsford *et al.*, 2022).

TREATMENT

Effective treatment of foreign bodies in the respiratory tract in children is crucial to mitigate the risks associated with upper airway obstruction, which can be potentially fatal. Early interventions not only improve the patient's prognosis but also reduce the time of exposure to complications such as atelectasis, infection, and structural damage to lung tissues (Morice *et al.*, 2020). Rapid intervention is essential to prevent severe respiratory sequelae and promote long-term quality of life for pediatric patients.

The main therapeutic approaches for removing foreign bodies from the airway include endoscopic techniques, such as bronchoscopy, which allows direct visualization of the foreign body and its removal using specialized instruments, ensuring precise intervention and minimizing additional damage to lung tissue (Ngamsanga *et al.*, 2023).

The choice between rigid and flexible bronchoscopy depends on the location of the object, the patient's age, and the interventional physician's expertise (Wu *et al.*, 2020). Rigid

bronchoscopy is preferred for large or irregularly shaped foreign bodies, allowing direct and precise intervention to keep the airway unobstructed in emergency situations (Wu *et al.*, 2020; Wiemers *et al.*, 2023). On the other hand, flexible bronchoscopy is more indicated for foreign bodies in hard-to-reach areas or in patients with complex anatomy (Han *et al.*, 2022; Schramm *et al.*, 2022).

In addition to traditional endoscopic techniques, cryotherapy has emerged as a promising option in specific situations, prioritizing tissue preservation and minimizing damage, with a low rate of reported adverse complications (Sapsford; Dawson and Anderson, 2022). The selection of the ideal therapeutic approach is based on a detailed evaluation of each clinical case, ensuring personalized treatment for patients with airway obstruction (Sezer; Eliçora and Topçu, 2024).

In recent years, flexible fiberscopes have played an increasing role in managing airway foreign bodies, allowing the use of specialized tools such as ultrathin basket-shaped forceps, facilitating the removal of objects through the working channel (Bohadana; Santos; Magalhães and Cesar, 2023). Various complementary technologies can be employed during flexible bronchoscopy, adapting to the specific nature of the foreign body, including special forceps, net baskets, freezing, balloons, and lasers. In complex situations, when foreign bodies resist conventional endoscopic methods and present an increased risk of complications such as severe hemoptysis or airway perforation, surgical intervention becomes inevitable (Han *et al.*, 2022).

For patients with clinical suspicion of a foreign body but without defined location by imaging or initial bronchoscopy, hydrosoluble contrast bronchography associated with flexible bronchoscopy can be an effective diagnostic and therapeutic approach (Bohadana; Santos; Magalhães and Cesar, 2023). Contrast bronchography provides a detailed visualization of the respiratory tree, facilitating the precise location of the impacted foreign body (Bohadana; Santos; Magalhães and Cesar, 2023). For cases of unilateral upper airway obstruction by a foreign body, the technique known as mother's kiss has proven effective, where the caregiver blocks the unaffected nostril and, with a sealed mouth, provides a burst of air into the child's mouth, facilitating object removal (Sapsford; Dawson; Anderson, 2022). In situations of total airway obstruction, the Heimlich maneuver has been effective, especially outside the hospital environment (Sezer; Eliçora and Topçu, 2024).

The combined use of flexible bronchoscopy with various specialized therapeutic techniques has demonstrated a satisfactory safety profile, with few reports of severe complications such as hemoptysis, dyspnea, and pneumothorax (Han *et al.*, 2022). If the initial attempt with the mother's kiss technique is unsuccessful, it is imperative to immediately refer the patient for evaluation in an emergency service (Sapsford; Dawson and Anderson, 2022). After combined hydrosoluble contrast bronchography and flexible bronchoscopy procedures, patient observation in an intensive care unit for 24 hours is recommended due to the potential for complications such as infection, perforation, or pneumonia (Bohadana;

Santos; Magalhães and Cesar, 2023). According to a recent review, no admissions to intensive care units or deaths related to cryotherapy complications have been reported, indicating a good safety profile for this emerging treatment (Schramm *et al.*, 2022). This adjustment aims to provide a comprehensive and updated overview of treatment strategies for airway obstruction by foreign bodies in children, highlighting the importance of the careful choice of the therapeutic approach for each specific clinical situation.

REFERENCES

BOHADANA, Saramira Cardoso; SANTOS, Rayza Gaspar dos; MAGALHÃES, Mirella Kalyne Cavalcante; CESAR, Regina Grigolli. Foreign body accidents in a pediatric emergency department. **International archives of otorhinolaryngology**, v. 27, p. 316-323, 2023.

DING, Guodong et al. Tracheobronchial foreign body aspiration in children: A retrospective single-center cross-sectional study. **Medicine**, v. 99, n. 22, p. e20480, 2020.

FASSEEH, Nader A. et al. A new scoring system and clinical algorithm for the management of suspected foreign body aspiration in children: a retrospective cohort study. **Italian Journal of Pediatrics**, v. 47, p. 1-9, 2021.

GOYAL, Samarth et al. Clinical variables responsible for early and late diagnosis of foreign body aspiration in pediatrics age group. **Journal of cardiothoracic surgery**, v. 15, p. 1-6, 2020.

HAN, Lin-Lin et al. Clinical analysis of bronchoscope diagnosis and treatment for airway foreign body removal in pediatric patients. **Italian Journal of Pediatrics**, v. 48, n. 1, p. 159, 2022.

LEE, Ji Hyuk. Foreign body ingestion in children. **Clinical endoscopy**, v. 51, n. 2, p. 129, 2018.

MORICE, Alyn H. et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. **European Respiratory Journal**, v. 55, n. 1, 2020.

NGAMSANGA, Satanee et al. Pediatric respiratory tract foreign bodies in children: A systematic review. **Auris Nasus Larynx**, v. 50, n. 4, p. 607-613, 2023.

OLIVA, Salvatore et al. Foreign body and caustic ingestions in children: a clinical practice guideline. **Digestive and Liver Disease**, v. 52, n. 11, p. 1266-1281, 2020.

PARVAR, Seyedeh Yasamin et al. The characteristics of foreign bodies aspirated by children across different continents: A comparative review. **Pediatric pulmonology**, v. 58, n. 2, p. 408-424, 2023.

SALIH, Alaaddin M.; ALFAKI, Musab; ALAM-ELHUDA, Dafalla M. Airway foreign bodies: A critical review for a common pediatric emergency. **World journal of emergency medicine**, v. 7, n. 1, p. 5, 2016.

SAPSFORD, Tim; DAWSON, Blake; ANDERSON, Daniel. Approach to paediatric nasal obstruction. **Australian Journal of General Practice**, v. 51, n. 10, p. 787-791, 2022.

SCHRAMM, Dirk et al. Cryotherapy in the paediatric airway: indications, success and safety. **Respirology**, v. 27, n. 11, p. 966-974, 2022.

SEZER, Hüseyin Fatih; ELIÇORA, Aykut; TOPÇU, Salih. Foreign body aspirations with rigid bronchoscopy and esophagoscopy in children. **Turkish Journal of Thoracic and Cardiovascular Surgery**, v. 32, n. Suppl1, p. S55, 2024.

SPEIDEL, Arne Jorma; WÖLFE, Lena; MAYER, Benjamin; POSOVSKY, Carsten. Increase in foreign body and harmful substance ingestion and associated complications in children: a retrospective study of 1199 cases from 2005 to 2017. **BMC pediatrics**, v. 20, p. 1-10, 2020.

TRUONG, Brandon; LUU, Kimberly. Diagnostic clues for the identification of pediatric foreign body aspirations and consideration of novel imaging techniques. **American Journal of Otolaryngology**, v. 44, n. 4, p. 103919, 2023.

WU, Yuhao et al. Delayed diagnosis and surgical treatment of bronchial foreign body in children. **Journal of Pediatric Surgery**, v. 55, n. 9, p. 1860-1865, 2020.

WIEMERS, Anna et al. Complication rates in rigid vs. flexible endoscopic foreign body removal in children. **International Journal of Pediatric Otorhinolaryngology**, v. 166, p. 111474, 2023.

Chapter 16

ACUTE POISONING IN PEDIATRICS

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Childhood poisoning is defined as a set of signs and symptoms triggered by acute exposure to chemical substances in excessive or inappropriate doses. Common in medical emergencies, poisonings can occur through ingestion, absorption, inhalation, or application of substances that come into contact with the body in harmful quantities (Lee *et al.*, 2019). The main

causes of poisoning in children and adolescents include medications, cleaning products, and pesticides (Vilaça; Volpe; Ladeira, 2019). It's crucial to note that most poisonings are preventable, often resulting from improper storage of items outside their original packaging, frequently without caps, in accessible places like kitchen cabinets or bedrooms (Mintegi *et al.,* 2019).

The incidence of accidental poisonings is higher in boys aged 0 to 5 years, while intentional poisonings are more common in girls aged 11 to 17 years (Vilaça; Volpe and Ladeira, 2019). These data underscore the impact of poisonings as a public health problem, with morbidity, mortality, and hospitalizations increasing significantly with age. The correlation between the prevalence of intentional poisonings and suicide is notable, especially involving psychotropic medications like benzodiazepines and opioids, often prescribed for psychiatric disorders and chronic pain (Land *et al*., 2020). These drugs, due to their low lethal dose and easy accessibility in both hospital and outpatient settings, present a significant challenge for reducing these rates, requiring restrictive legislation and multidisciplinary approaches to understand the psychodynamic aspects of this life stage.

In the context of accidental poisonings, it is crucial to consider cases where poisoning may be asymptomatic, with lead being a notable toxin. Lead, found in paints, household dust, contaminated water, and soil, has no biological function in the body and is associated with neurocognitive and behavioral dysfunctions in child development. Although many cases are asymptomatic, symptoms like headache, abdominal pain, anorexia, and constipation indicate an emergency requiring immediate hospitalization of the child (Mayans, 2019).

The diagnosis of pediatric poisoning is based on the initial clinical evaluation through a detailed history. Emergency services must be updated on managing these situations, using nationally unified guidelines, protocols, and toxicological-pharmacological information systems (Kazanasmaza; Kazanasmaza; Çalıkb, 2019). Treatment mainly aims to provide clinical and hemodynamic support to the patient, identifying the toxidrome to determine the need for decontamination with antidotes or dilution through volume replacement (Mayans *et al*., 2019; Kazanasmaza *et al*., 2019; Lee *et al*., 2019).

EPIDEMIOLOGY

Acute poisoning is a global problem that is quite common in pediatric age. It is estimated that accidental poisonings cause about 45,000 annual deaths in children and adolescents, with an incidence of 1.8 per 100,000 inhabitants (Vilaça; Volpe; Ladeira, 2019). Recent data indicate that approximately 32.6% of poisoned children worldwide are under 3 years old, and 44.2% are under 5 years old (Soave *et al*., 2022).

Nationally, studies show that most accidents occur at home, especially among boys under four years old, with medications and cleaning products being the main substances involved (Vilaça; Volpe and Ladeira, 2019). According to Gokalp (2019), 46.6% of accidental poisoning cases involve cleaning products, and 38% involve medications.

Although fatal childhood poisonings have significantly decreased in recent decades (Mintegi *et al*., 2019), they remain a frequent cause of emergency consultations. A general trend in the prevalence and incidence of acute pediatric poisoning over time can be observed, considering variables such as environment, mode of poisoning, and type of toxic substance. Most cases of acute pediatric poisoning in emergency care occur unintentionally at home, through oral ingestion of medications and cleaning products (Vilaça; Volpe; Ladeira, 2019). Factors such as increased medical prescriptions for adults, work fatigue associated with reduced caregiver vigilance in the afternoon and evening, and improper storage of substances contribute to these events (Soave *et al*., 2022).

According to Lee *et al*. (2019), pediatric poisoning can be classified as unintentional, predominantly occurring in children under 5 years old due to longer stays at home, and intentional, more common in adolescents, often associated with suicidal or recreational practices, with a higher incidence among female adolescents (Soave *et al*., 2022). Unintentional poisonings are often related to the consumption of medications, cleaning products, pesticides, cosmetics, and plants (Lee *et al*., 2019), due to the accessibility of these substances and children's imitative behavior. It is the responsibility of caregivers to ensure the safety of these locations using secure packaging and proper storage (Gokalp, 2019). In the case of unintentional drug poisonings, the most commonly involved drugs are benzodiazepines, analgesics, and antiepileptics (Vilaça; Volpe and Ladeira, 2019).

It is important to note that although acute pediatric poisoning represents a serious medical emergency, it rarely results in death or prolonged hospitalization, both nationally and globally (Vilaça; Volpe and Ladeira, 2019; Mintegi *et al*., 2019). This can be attributed to the low lethality of predominant substances like medications and chemicals. Another relevant aspect is the significant change in pediatric poisoning patterns when considering the adolescent age group, with intentional cases predominating among female adolescents. This distribution varies globally, with distinct incidence peaks, being more common in North America and the Western Pacific regions (Mintegi *et al*., 2019).

DIAGNOSIS

Acute poisoning is one of the most common emergencies in children and a significant cause of accidental injuries due to its rapid onset and serious harm to child health. As highlighted by the World Health Organization (WHO), poisoning is among the top five causes of accidents in children (Zhang; Huo; Jing and Dong, 2024). Ghannoum and Roberts (2023) emphasize that proper and rapid management of poisonings can reduce both the severity and duration of the condition. Special vigilance is essential for adolescents, especially those who may intentionally ingest illicit drugs or alcohol, including investigating suicide attempts. For young children, particularly under 1 year old, attention should be paid to the possibility of forced ingestion or intentional poisoning, also assessing the potential for child abuse.

The initial approach should prioritize early diagnosis, patient stabilization, and investigation of the involved toxic agent. These steps are crucial for clinical evolution and outcomes and include obtaining a detailed clinical history, thorough physical examination, and performing complementary and toxicological tests, as discussed by Velez, Shepherd, and Goto (2020).

It is essential to quickly identify potentially lethal toxic agents and those with a delayed onset of clinical toxicity for appropriate interventions and complication prevention, as highlighted by Ghannoum and Roberts (2023). Managing the poisoned child depends on the time of exposure, detection of involved toxins, and clinical presentation, which is crucial for decisions like gastrointestinal decontamination and administration of antidotal therapy when indicated.

The clinical history should be meticulously collected, preferably involving witnesses of the exposure or family members. It is crucial to inquire about pre-existing medical conditions and medication use to investigate potential cases of unintentional overdose. Additionally, detailed information about the toxic exposure, including involved substances, mode of exposure, correlation with presented signs and symptoms, and any expected laboratory findings of acute poisoning, must be obtained, as described by Velez, Shepherd, and Goto (2020).

Acute poisonings in pediatrics present a diversity of signs and symptoms, varying according to the involved toxic agent and the exposure route. As discussed by Hon, Hui, and Leung (2021), anticholinergic poisoning can trigger a range of peripheral and central manifestations, including tachycardia, hyperthermia, non-reactive mydriasis, dry mucous membranes, gastrointestinal effects, and neurological symptoms like delirium, confusion, and visual hallucinations.

On the other hand, carbon monoxide exposure in children, as described in the same study, can start with symptoms like headache, dizziness, and malaise. High COHb levels can cause more severe symptoms such as vomiting, visual disturbances, confusion, and even loss of consciousness.

Additionally, cholinergic poisoning, as observed by Hon, Hui, and Leung (2021), manifests with a wide range of symptoms, including bradycardia, bronchorrhea, lacrimation, excessive salivation, gastrointestinal hyperactivity, and miosis, along with central symptoms like seizures and coma in severe cases. Cyanide poisoning, as highlighted by Wong and Baum (2019), is characterized by signs like tachypnea, tachycardia, abdominal pain, and confusion.

Cannabis poisoning, as discussed by Wong and Baum (2019), can result in neurological manifestations like drowsiness and coma, along with cardiovascular, respiratory, and gastrointestinal symptoms. Children exposed to pesticides, as observed by Zhang, Huo, Jing, and Dong (2024), often present symptoms like vomiting, abdominal pain, and neurological disturbances, demonstrating the diversity in clinical presentation of these

conditions. This variety of symptoms underscores the diagnostic complexity of pediatric poisonings and the crucial importance of a comprehensive and individualized clinical approach to managing these cases to minimize harm and optimize clinical outcomes.

Early diagnosis of acute poisoning in pediatrics plays a crucial role in effective management and reducing severe complications. According to Velez *et al.* (2020), the initial assessment should be quick and comprehensive, focusing on patient stabilization and identifying the involved toxic agent. This includes securing the airway, assessing breathing and circulation, and monitoring vital signs to identify early manifestations of toxicity. Detailed physical examination is essential to detect specific symptoms, such as stridor and salivation, indicative of significant esophageal damage after caustic agent ingestion, as described by Niedzielski *et al.* (2020).

Additionally, flexible nasolaryngoscopy and endoscopy are crucial tools for evaluating laryngeal and esophageal injuries, respectively, allowing precise diagnosis of the injury degree and planning appropriate treatment. Early esophageal endoscopy is recommended within the first 24 to 48 hours after caustic ingestion unless contraindications like suspected perforation or epiglottis swelling are present, as evidenced by the practice described by Niedzielski *et al.* (2020).

In cases of unknown ingestion, as mentioned by Wong and Baum (2019), it is prudent to perform an electrocardiogram, a serum toxicology panel, and a urine drug screen, especially to identify co-ingestions that may influence clinical management. This multidisciplinary approach in early diagnosis not only improves clinical outcomes but also guides the implementation of specific therapeutic measures for each case of acute poisoning in children.

As conceptualized by Velez *et al.* (2020), toxic exposure should be considered in the differential diagnosis of children presenting with acute onset of multi-organ dysfunction, altered mental state, respiratory or cardiac impairment, unexplained metabolic acidosis, seizures, or a puzzling clinical picture. Signs like hypoglycemia, hypoxemia, and shock can have various clinical causes besides acute poisoning and should be investigated and ruled out. It is crucial to recognize and address any trauma or underlying condition before initiating any toxic agent decontamination.

According to the study described by Wong and Baum (2019), the differential diagnosis for acute cannabis exposure is broad due to the variety of nonspecific neurological symptoms, such as altered behavior, lethargy, or coma, which can mimic conditions like postictal states, encephalitis, or sepsis. This emphasizes the importance of a detailed clinical history and exclusion of other causes of symptoms before confirming the diagnosis of cannabis poisoning.

Regarding new diagnostic techniques, neuron-specific enolase (NSE) is used to assess neurological changes in unexplained poisoning cases. NSE alterations are particularly useful as sensitive and specific biomarkers for brain injuries associated with drug poisoning, as evidenced by Zhang, Huo, Jing, and Dong (2024).

TREATMENT

Acute poisonings in pediatrics present a wide variety of etiological agents, each capable of triggering severe symptoms that can lead to death. Therefore, early diagnosis and recognition of the involved substance are extremely important to initiate appropriate therapeutic management as quickly as possible (Hon; Hui and Leung, 2021).

To initiate the management of any poisoning case, whether mild or severe, a thorough assessment of the patient's vital signs is fundamental. This includes checking the airway, breathing, circulation, and neurological function. Based on the identified signs, initial measures should be instituted individually and protocolarily. The main goal of these measures is to ensure the patient's hemodynamic stability and optimize renal function to improve the elimination of the ingested toxic agent. Possible interventions include orotracheal intubation, ventilatory support, fluid administration, inotropes, vasopressors, and specific medications such as benzodiazepines for controlling seizures and agitation. According to Das *et al.* (2020), these approaches are fundamental for effective initial management.

Urgent gastrointestinal decontamination aims to reduce the absorption of the poison in the body, thus improving the patient's prognosis and recovery. Before initiating this procedure, it is crucial to prevent aspiration in patients at risk, especially those with vomiting, decreased consciousness level, or seizures, through orotracheal intubation when indicated. The most common routes for gastrointestinal decontamination are nasogastric or orogastric, as guided by Das *et al.* (2020).

Activated charcoal is often used as the method of choice for gastrointestinal decontamination, ideally administered within two hours after poison ingestion. In cases of large exposures, the dose can be repeated every 2 to 4 hours. However, it is ineffective against acids, alcohols, metal ions like lithium and iron, as evidenced in scientific literature. In situations of highly toxic exposure or contraindication to activated charcoal, total intestinal irrigation with isotonic solution, such as polyethylene glycol, administered enterally in high volume (1L/h) until clear rectal effluent, can be chosen (Das *et al.*, 2020). This measure is essential for specific cases where traditional gastrointestinal decontamination is inadequate.

Antidotes are proven effective measures in the treatment of poisonings, characterized as direct or indirect agonists or antagonists of a specific poison. The use of these agents varies according to the type of ingested toxin and is generally indicated in cases of confirmed toxicity or high concentration of the identified agent. The dosage must be individually adjusted based on the patient's clinical response. Below is a table of the main antidotes frequently used in clinical practice (Das *et al*l., 2020):

Table 1.0: Antidotes are essential to neutralize the specific toxic effects of each agent.

Toxic Agent	Antidote
Acetaminophen	N-acetylcysteine
Anticholinergic medications	Physostigmine for significant delirium
Anticholinesterase insecticides	Atropine and possibly pralidoxime or obidoxime
β-adrenergic antagonists	Epinephrine, insulin-dextrose infusion
Benzodiazepines	Flumazenil
Calcium channel blockers	Calcium, insulin-dextrose infusion
Carbon monoxide	Oxygen
Cyanide	Hydroxocobalamin and/or thiosulfate
Dabigatran	Idarucizumab
Digoxin	Digoxin Fab antitoxin, atropine
Envenomation (e.g., snake, spider)	Antivenom
Ethylene glycol/methanol	Ethanol or fomepizole
Iron	Deferoxamine
Isoniazid	Pyridoxine
Methotrexate	Folinic acid, glucarpidase
Opioids	Naloxone
Methemoglobinemia induced by toxins	Methylene blue
Salicylates	Bicarbonate
Sulfonylureas	Octreotide, glucose
Tricyclic antidepressants	Bicarbonate
Valproic acid	L-carnitine
Warfarin	Vitamin K

Source: Das *et al*., 2020.

Urine alkalinization involves raising urine pH to facilitate the excretion of weak acidic poisons like salicylates, phenobarbital, and chlorpromazine. It is performed by administering sodium bicarbonate in bolus followed by 5% dextrose infusion. This technique requires strict monitoring due to the risk of complications like hypokalemia and hypernatremia (Das *et al*., 2020). Intestinal dialysis is a technique using multiple doses of activated charcoal to interrupt enterohepatic circulation or perform passive retro-diffusion from intestinal capillaries. It is effective against poisons like carbamazepine, phenobarbital, and quinine, and can also be applied to colchicine and salicylates (Das *et al*., 2020).

Extracorporeal Treatments:

1. **Hemodialysis:** A widely used method that removes poisons through a semipermeable membrane, suitable for toxins with a molecular weight above 10,000 Da. It is also indicated for correcting metabolic imbalances and replacing renal function (Das *et al.*, 2020).
2. **Hemofiltration:** Similar to hemodialysis, but allows the removal of larger poisons (up to 50,000 Da) using convection or solute and solvent drag (Das *et al.*, 2020).
3. **Hemoperfusion:** Uses activated charcoal or resins to adsorb poisons from the blood but has disadvantages like requiring intense anticoagulation and lower availability compared to hemodialysis (Das *et al.*, 2020).
4. **Continuous Renal Replacement Therapies (CRRTs):** Combines diffusion and convection for continuous removal of poisons, especially in intensive care units, though it is less efficient than hemodialysis and hemofiltration (Das *et al.*, 2020).
5. **Other Techniques:** Include peritoneal dialysis, therapeutic plasma exchange, and exchange transfusion, each with specific advantages and limitations for poison removal depending on the clinical case (Das *et al.*, 2020).

These approaches are fundamental for mitigating the harmful effects of acute poisoning, requiring careful evaluation to determine the best strategy according to the involved toxic agent and the patient's clinical condition.

The discussion on treating acute cannabis poisoning, it's a problem whose incidence is increasing in the pediatric population in states with decriminalization of recreational and medicinal cannabis use. The initial approach to the patient is based on supportive care. In cases where there is a risk of bronchoaspiration or apnea, especially in children, rapid orotracheal intubation followed by assisted mechanical ventilation should be considered. For lethargic patients, electrolyte, gasometry, and blood glucose evaluation are indicated. Fluid administration should be considered in the presence of signs of hypovolemia. Benzodiazepines are useful in cases of agitation, cannabis hyperemesis syndrome, or co-ingestion with cocaine and should be combined with measures such as reducing environmental stimuli. In severe cases, the use of flumazenil may be considered (Wong; Baum, 2019).

In cases where children have access to illicit drugs at home or pain medications like codeine, it is crucial to be alert for signs of opioid intoxication. Intravenous naloxone is indicated at an initial dose of 0.01 mg/kg, which can be repeated every 3-5 minutes until clinical response. Clinical observation for at least 24 hours is essential for patients with respiratory depression or reduced respiratory rate (Hon; Hui and Leung, 2021).

The incidence of antiepileptic drug poisoning has increased, but there are no specific guidelines for management, which is limited to support. Cardiological monitoring, comprehensive laboratory tests, and serum level measurement of the involved agent are recommended. Measures like gastric lavage and activated charcoal may be considered in recent poisonings but are less effective with carbamazepine. Extracorporeal techniques like hemodialysis are reserved for severe cases (Ferranti *et al.*, 2018).

In carbon monoxide exposure, initial therapy with 100% oxygen is fundamental, while the use of hyperbaric oxygen is controversial due to the scarcity of evidence. For cyanide poisoning, management includes sodium nitrite followed by sodium thiosulfate and hydroxocobalamin (Hon; Hui and Leung, 2021).

Poisoning by anticholinergics, cholinergics, benzodiazepines, and acetaminophen requires specific treatment. Physostigmine is recommended for anticholinergic poisoning, while atropine is used in cholinergic poisonings. Flumazenil may be necessary in benzodiazepine poisonings, except in cases of known seizure syndrome. N-acetylcysteine is crucial for acute acetaminophen toxicity (Hon *et al*., 2021).

Acute poisoning by corrosive substances is common in young children due to accidental ingestion. Initial management includes stabilization of the airway, cardiovascular system, and neutralization of the substance. Subsequent therapy may involve intravenous fluid therapy and parenteral nutrition. The use of proton pump inhibitors and vitamin E has proven effective in some cases, while the use of steroids and prophylactic antibiotics is controversial (Niedzielski *et al*., 2020; Das *et al*., 2020).

Treating acute poisoning in children requires a specific and differentiated approach, focusing on general support and, when necessary, targeted therapeutic measures. Early diagnosis is crucial to initiate appropriate management and minimize complications. Proper patient stratification can reduce admissions to pediatric ICUs, providing significant improvements in clinical and emotional outcomes for patients and families (Patel *et al*., 2018).

REFERENCES

DAS, Saibal *et al*. Prophylactic use of steroids and antibiotics in acute hydrocarbon poisoning in children. **Journal of pharmacy practice**, v. 33, n. 1, p. 90-95, 2020.

FERRANTI, Silvia *et al*. Antiepileptic drugs: Role in paediatric poisoning. **Journal of Paediatrics and Child Health**, v. 54, n. 5, p. 475-479, 2018.

GHANNOUM, Marc; ROBERTS, Darren M. Management of poisonings and intoxications. **Clinical journal of the American Society of Nephrology**, v. 18, n. 9, p. 1210-1221, 2023.

GOKALP, Gamze. Evaluation of poisoning cases admitted to pediatric emergency department. **International Journal of Pediatrics and Adolescent Medicine**, v. 6, n. 3, p. 109-114, 2019.

HON, Kam Lun; HUI, Wun Fung; LEUNG, Alexander Kc. Antidotes for childhood toxidromes. **Drugs in context**, v. 10, 2021.

KAZANASMAZ, Halil; KAZANASMAZ, Özlem; ÇALIK, Mustafa. Epidemiological and sociocultural assessment of childhood poisonings. **Turkish journal of emergency medicine**, v. 19, n. 4, p. 127-131, 2019.

LAND, Megan E. *et al*. Analysis of 207,543 children with acute opioid poisonings from the United States National Poison Data System. **Clinical toxicology**, v. 58, n. 8, p. 829-836, 2020.

LEE, Jung *et al*. Clinical spectrum of acute poisoning in children admitted to the pediatric emergency department. **Pediatrics & Neonatology**, v. 60, n. 1, p. 59-67, 2019.

MAYANS, Laura. Lead poisoning in children. **American family physician**, v. 100, n. 1, p. 24-30, 2019.

MINTEGI, Santiago *et all*. International epidemiological differences in acute poisonings in pediatric emergency departments. **Pediatric emergency care**, v. 35, n. 1, p. 50-57, 2019.

NIEDZIELSKI, Artur *et al* Caustic agents ingestion in children: a 51-year retrospective cohort study. **Ear, Nose & Throat Journal**, v. 99, n. 1, p. 52-57, 2020.

PATEL, Meral M. *et al*. Reducing childhood admissions to the PICU for poisoning (ReCAP2) by predicting unnecessary PICU admissions after acute intoxication. **Pediatric critical care medicine**, v. 19, n. 2, p. e120-e129, 2018.

SOAVE, Paolo Maurizio *et al*. Acute poisoning in children admitted to pediatric emergency department: a five-years retrospective analysis. **Acta Bio Medica: Atenei Parmensis**, v. 93, n. 1, 2022.

VELEZ, Larissa I.; SHEPHERD, J. Greene; GOTO, C. S. Approach to the child with occult toxic exposure. **UpToDate ONLINE**, v. 15, 2020.

VILAÇA, Luciana; VOLPE, Fernando Madalena; LADEIRA, Roberto Marini. Accidental poisoning in children and adolescents admitted to a referral toxicology department of a Brazilian emergency hospital. **Revista Paulista de Pediatria**, v. 38, p. e2018096, 2019.

WONG, Kei U.; BAUM, Carl R. Acute cannabis toxicity. **Pediatric emergency care**, v. 35, n. 11, p. 799-804, 2019.

ZHANG, Huajun *et al*. Clinical analysis of acute poisoning in children. **BMC pediatrics**, v. 24, n. 1, p. 212, 2024.

Chapter 17

ACCIDENTS WITH VENOMOUS ANIMALS

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CHAPTER 17

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Accidents involving venomous animals such as snakes, scorpions, and spiders represent a significant public health problem, especially frequent in rural areas of tropical countries. These incidents result from the injection of toxic substances by animals, triggering severe reactions in the human body, with generally more severe impacts on children than adults, which is particularly alarming in the pediatric

context. While in Europe reporting these events is not mandatory, in Brazil they have been considered compulsory notifications since 2010, reflecting the seriousness and prevalence of the problem (Konstantyner *et al.*, 2022; Silva, Bernade, and Abreu, 2015; Paolino *et al.*, 2023).

The World Health Organization (WHO) included snakebite envenoming on the list of Neglected Tropical Diseases in 2009. In Brazil, the incidence rates of accidents with venomous animals have increased, except in the Southern region, where incidents are less frequent. Scorpions and snakes are the most common culprits, especially among individuals aged 10 to 19 years. However, approximately 90% of snake bites and spider bites do not have the animal's genus identified, which hinders investigation and appropriate treatment since each species requires specific management approaches due to their toxins (Konstantyner *et al.*, 2022; Silva, Bernade and Abreu, 2015; Amado *et al.*, 2021; Santana *et al.*, 2020).

In severe cases of envenomation by armed spiders, neurological and cardiac complications may occur due to the venom's toxicity to these systems. In scorpion envenomations, variables such as the type of venom, number of stings, and injected quantity can influence the outcome, potentially leading to complications like pulmonary edema or cardiac dysfunction. Regardless of the involved animal, early identification and proper patient management are crucial to increasing survival chances (Konstantyner *et al.*, 2022; Silva, Bernade and Abreu, 2015; Amado *et al.*, 2021; Santana *et al.*, 2020).

Studies indicate that the number of accidents with venomous animals is likely to increase in the future due to climate change, which will result in greater interaction between humans and these animals, altering the ecology and geographic distribution of species and consequently increasing the morbidity and mortality associated with these accidents (Paolino *et al.*, 2023).

The pediatric population is particularly vulnerable to these accidents due to their natural curiosity and lower capacity for self-protection, in addition to physiological differences that can intensify venom toxicity. Current trends indicate a growing demand for prevention policies, training of healthcare professionals for effective diagnosis and treatment, as well as educational campaigns targeted at at-risk communities to reduce the morbidity and mortality related to these accidents. Implementing prevention methods and effective public policies can mitigate this problem (Forrester *et al.*, 2018).

EPIDEMIOLOGY

Accidents involving venomous animals are frequent and continue to grow, representing a significant public health concern, especially in tropical countries like Brazil. From 2007 to 2019, 2,164,654 cases of venomous animal accidents were reported in Brazil (Tomaz, Soares, & Bonfada, 2023), of which 594,447 occurred among children and

adolescents, reflecting a 122.5% increase in the annual number of cases from 2007 to 2019 (Konstantyner *et al.*, 2022). Among venomous animals, snakes, scorpions, and spiders are the most prevalent and lethal.

Snakes are responsible for approximately 29,000 cases per year and an average of 125 deaths, with Jararacas accounting for 86.23% of reported cases (Silva, Bernade and Abreu, 2015). In 2013, spider envenomations totaled 27,125 annual cases, with 36 resulting in death, while scorpion stings resulted in 69,036 cases, with 80 deaths (Silva, Bernade and Abreu, 2015).

Accidents with venomous animals vary according to age group, gender, geographic region, and involved species, with greater severity observed in children under 10 years old (Silva; Bernade and Abreu, 2015). In Brazil, 55% of victims in the pediatric range are between 10 and 19 years old, except in the Southern region, where the prevalence is higher in children aged 0 to 9 years. The Northeast region has the highest incidence, with 74.26% of cases in children aged 0 to 9 years and 82.44% in young people aged 10 to 19 years (Konstantyner *et al.*, 2022).

There are significant variations in the species of venomous animals according to each region of Brazil. In the North, snakes predominate, responsible for 60% of local accidents, while in the South, there is a prevalence of spider envenomations, affecting 47.94% of children. In the Southeast, Midwest, and Northeast, scorpion stings are more common (Konstantyner *et al.*, 2022).

The incidence of accidents with venomous animals in populations composed of adolescents and children establishes an outstanding epidemiological and statistical scenario in the field of pediatric emergency and urgency, considering the vulnerability of this group. This population set exhibits unique epidemiological characteristics, with an exponentially growing trend of these accidents in the age range of 10 to 19 years in all regions of Brazil. Incidents with scorpions, snakes, and spiders stood out as the most prevalent in this clinical population analysis. Therefore, specialized medical attention is crucial in these situations, given the potential severity of the condition (Konstantyner *et al.*, 2022).

Prevention initiatives for these accidents have shown potentially positive results, improving therapeutic approaches to these conditions. Early diagnosis associated with immediate treatment, observing the patient's clinical characteristics and knowledge of the epidemiological profile, are directly related to more favorable clinical outcomes. Thus, the importance of socio-educational actions directed at the population and effective public health policies is emphasized, aiming to reduce the potentially fatal outcomes of accidents with venomous animals in children and adolescents (Konstantyner *et al.*, 2022).

Historically, accidents with venomous animals, such as snake bites, were treated with traditional remedies and rudimentary medical practices, resulting in high mortality rates. In the 19th and 20th centuries, advances in medicine, such as the development of specific antivenoms, revolutionized the management of these incidents (Forrester, Weiser,

& Forrester, 2018). In the 1980s, there was a significant increase in the documentation and research on snake bites, especially in the United States, where national databases were established to monitor these cases (Greene; Folt; Wyatt and Brandehoff, 2021). Today, the epidemiology of snake bites and other venomous animal accidents is well understood. Most bites occur in rural and suburban areas, with few deaths in the United States due to better access to medical care and the use of antivenoms. Rattlesnakes and copperheads are responsible for most envenomations, while bites from non-native snakes are rare and occur mainly in private collections and zoos (Forrester; Weiser and Forrester, 2018).

Between 2008 and 2015, there were 1,610 animal-related deaths in the U.S., with most caused by non-venomous animals. Deaths caused by hymenoptera (wasps, bees, and ants) remained stable, while mortality from snake bites is very low, with about 9,900 annual envenomations and a mortality rate of only 0.05% (Greene; Folt; Wyatt and Brandehoff, 2021).

Geographic location is one of the main risk factors, with rural and suburban areas near the natural habitat of these animals presenting a higher incidence of bites. Additionally, climatic conditions play a crucial role, with more incidents occurring in warmer months when people are more outdoors (Silva; Bernade and Abreu, 2015). Activities like camping, gardening, and farming increase the risk, as does handling venomous animals in controlled environments (Forrester; Weiser and Forrester, 2018). Limited access to medical care in remote areas exacerbates the consequences of these accidents, while a lack of education on prevention and first aid contributes to the severity of incidents. Alcohol or drug consumption can result in risky behaviors, increasing vulnerability (Greene, Folt, Wyatt and Brandehoff, 2021). Men and people of productive age are at greater risk due to higher occupational and recreational exposure, while children and the elderly are more vulnerable to severe complications (Konstantyner *et al*., 2022).

DIAGNOSIS

Healthcare professionals often face challenges in accurately identifying snakes, as they are not experts in this field, which can lead to inadequate treatment of the victim. Given the acute nature of snakebite envenoming, it is crucial to quickly identify and administer the appropriate treatment, such as antivenom and ventilatory support. Although immunoassays and molecular tools exist to identify specific snake species, they are limited by high cost, need for specialized technicians, and low specificity, currently restricted to Australia and Papua New Guinea. Rapid diagnostic tests are in development, but their effectiveness in low- and middle-income countries remains uncertain. The syndromic approach is common in managing snakebite envenoming, aiding in species identification, though it also presents limitations (De Castañeda *et al*., 2019).

A snakebite, whether from a venomous or non-venomous snake, triggers anxiety, fear, and other autonomic manifestations (e.g., nausea, vomiting, tachycardia, diarrhea,

diaphoresis), which can be difficult to distinguish from systemic envenoming symptoms. The severity of envenoming is categorized as minimal, moderate, or severe, based on local findings, systemic signs, coagulation tests, and laboratory results. The evaluation should prioritize the most severe symptoms, signs, or laboratory findings, given the potential rapid progression of envenoming from minimal to severe, requiring continuous reevaluation (Silva *et al.*, 2017).

Loxoscelism, triggered by bites from Loxosceles spiders, requires diagnostic precision through the collection and identification of the spider. Only 23.3% of reported cases are confirmed by identification or immunoassay (ELISA), with most being presumed. The local and systemic symptoms of loxoscelism are not specific and can be confused with other conditions. In cases where the spider is not collected, the diagnosis is probable, supported by clinical manifestations. Understanding the disease course is crucial for presumptive diagnoses where the spider is not observed. Geography also influences, with misreports of loxoscelism in areas without documented presence of the spiders (Lopes, Squaiella-Baptistão and Marques and Tambourgi, 2020).

Laboratory tests complement the diagnosis of loxoscelism, such as hematologic, hemostatic, and biochemical tests, excluding other conditions and monitoring the disease. Besides ELISA, Coombs tests, cultures, and imaging exams are used to assess systemic and local complications. Urinalysis is crucial to detect complications like severe intravascular hemolysis. Cutaneous-hemolytic loxoscelism is monitored by the evolution of skin and adjacent tissue lesions, guiding appropriate treatment (Lopes; Squaiella-Baptistão; Marques and Tambourgi, 2020).

Scorpions also represent a serious public health problem related to accidents involving venomous animals. In Brazil, four species of the Tityus genus are responsible for most envenomations: *T. serrulatus, T. stigmurus, T. bahiensis,* and *T. obscurus*. In the Brazilian Amazon, where these species are prevalent, their toxins are extremely potent. The *Tityus* genus comprises 27 species, distributed in four subgenera, six of which are associated with human envenomations: *T. bastosi, T. silvestris, T. apicans, T. matthieseni, T. metuendus*, and *T. obscurus*. Although these species are mainly found in forest environments, they occasionally invade domestic areas, especially *T. metuendus*. There is a predominance of adult males causing envenomations, probably due to more intense activity in search of food and partners, while females tend to remain sheltered during pregnancy or lactation periods (Gomes *et al.*, 2020).

Most envenomations occur in men of all age groups, with a particular prevalence among those aged 40 to 49 years, often affecting the feet and hands. Clinical data include venom classification, local and systemic signs and symptoms, antivenom use, the number of vials administered, and complementary laboratory tests. Stings are classified as: 1. Dry, without local or systemic manifestations; 2. Class I: only local manifestations; 3. Class II: non-severe systemic manifestations; 4. Class III: life-threatening manifestations. The

most common local and systemic symptoms include nausea (9.3%), myoclonus (8.6%), occasional vomiting (7.3%), lethargy (6.0%), tachycardia (4.6%), and tachypnea (4.6%). The most frequent local manifestations include pain (84.1%), paresthesia (34.4%), mild edema (25.8%), and hyperemia (21.9%). Severe symptoms include dyspnea, hypotension, profuse vomiting, and seizures, indicating severity. The analysis revealed that clinical manifestations are similar among patients stung by different species of scorpions. Patients envenomed by T. apicans often present piloerection and myoclonus, described by patients as a "sensation of electric shock" throughout the body (Gomes *et al.*, 2020).

TREATMENT

Studies highlight the urgency of prompt and effective management to increase survival and reduce complications in cases of envenomation by venomous animal bites, as evidenced by more than 5.4 million snakebite cases globally, resulting in nearly 138,000 deaths and 400,000 sequelae (Pucca *et al.*, 2020). The diversity of therapeutic approaches reflects the lack of a universally accepted standard, requiring the continuous development of effective, accessible, and low-cost treatments (Fry, 2018). Proper management depends on a multidisciplinary approach and consideration of epidemiology, ranging from supportive therapies like saline solution, antivenom, and systemic steroids to surgical interventions like fasciotomy and dermatotomy in severe cases, as well as dermatological management to prevent cutaneous necrosis complications (Di Nicola *et al.*, 2021). This study will address the importance of precise care, management strategies, and new therapies, exploring their risks and benefits.

Studies highlight the urgency of prompt and effective management to increase survival and reduce complications in cases of envenomation by venomous animal bites, as evidenced by more than 5.4 million snakebite cases globally, resulting in nearly 138,000 deaths and 400,000 sequelae (Pucca *et al.*, 2020). In the prehospital environment, it is crucial to follow WHO (2016) recommendations to remove tight objects around the bite area, reassure the victim to avoid movements that may accelerate venom spread, immobilize the affected area, and apply a moderate compression bandage. Analgesics like acetaminophen are administered according to specific dosage guidelines for local pain relief, while measures to prevent complications like vomiting are also essential. Immediate transport to a healthcare facility capable of administering antivenom and other care is recommended (Fry, 2018).

In the hospital environment, evaluating tetanus immunization and other immunizations is a priority (Fry, 2018; Di Nicola *et al.*, 2021). Specific treatment involves administering antivenom, composed of essential polyclonal antibodies to neutralize the venom and prevent irreversible organ damage (Pucca *et al.*, 2019). The decision to administer antivenom should be quick and careful, especially in the presence of systemic envenomation signs or severe and progressive local symptoms, due to potential adverse side effects. Early

antivenom administration, preferably within 1 to 2 hours after the bite, is crucial to optimize its efficacy. The intravenous route is preferred due to its higher bioavailability, allowing the antivenom to reach up to 85% of the venom inoculation site within 2 hours. Dosage varies, generally administering 1 to 2 vials, although there is controversy over the ideal dosage, administration frequency, and treatment duration. Children require dosing based on the amount of venom injected, with specific guidelines still under debate (Le Geyt *et al.*, 2021).

Local symptom management involves careful clinical evaluation of vesicles and blisters to monitor the extent of underlying necrosis. Cleaning and immobilizing the affected area are essential, using solutions like hydrogen peroxide, known for its effectiveness in dissolving venom. Compartmental pressure should be regularly monitored to detect early complications. Patients should be kept under continuous observation in the healthcare unit, with periodic laboratory and clinical investigations, including coagulation tests, complete blood count, urinalysis, liver function, blood glucose, and renal function within the first 24 hours, along with constant physical and vital monitoring. Discharge can be considered for patients who respond well to treatment and show clinical improvement, with recommendations for post-discharge follow-up and periodic reevaluation (Nelson *et al.*, 2019; Di Nicola *et al.*, 2021).

There are various antivenoms available, each with unique tissue penetration and body clearance characteristics (Fry, 2018). Monovalent antivenom is preferred when the snake species is identified, allowing more targeted treatment, while polyvalent antivenom is more widely used due to its effectiveness against multiple species. For complications like ulcers or cutaneous necrosis, adequate washing followed by debridement when necessary is recommended, with regular dermatological follow-up to avoid additional complications (Mercuri *et al.*, 2018, 2020). Broad-spectrum antibiotic prophylaxis is indicated in cases of acute infection or high risk of secondary infections. Options include amoxicillin, cephalosporins, azithromycin, metronidazole, trimethoprim + sulfamethoxazole (Di Nicola *et al.*, 2021). Fasciotomy is not recommended without evidence of critical compartmental pressure increase (Fry, 2018; Hamza *et al.*, 2021).

New approaches are being explored to improve the distribution and implementation of therapies for snakebites. Animal studies have shown potential reversal of symptoms like coagulopathy and neurotoxicity with therapeutic agents like marimastat and varespladib, though their effectiveness in humans still needs confirmation. Current antivenom distribution strategies include the “hub-and-spoke” model, where rural facilities are connected to central hospitals in urban areas, ensuring rapid access to antivenoms and specialized support (Hamza *et al.*, 2021).

Innovative approaches are being explored to improve the safety and efficacy of antivenoms. The continuous reassessment method (CRM) of 3 + 3 dose escalation has been successfully used to introduce antivenoms, although it has received criticism and suggestions for modifications. Recently, an adaptive design based on the Bayesian model

was developed, more efficient and flexible, using sequential patient data to continuously optimize the ideal, safe, and effective antivenom dose, as demonstrated in the treatment of Russell's viper envenoming. These advances are expected to lead to the development of more effective antivenoms against a wide variety of snake species, such as the idealized pan-African polyvalent antivenom. Improvements in production, implementation of Good Manufacturing Practices (GMP), and the introduction of WHO's antivenom prequalification program are fundamental strategies to increase the safety, efficacy, and accessibility of these products globally (Hamza *et al.*, 2021).

With advances in recombinant DNA technology, there is a significant opportunity to develop new antidotes based on recombinant antibodies and antibody fragments (Laustsen *et al.*, 2020). Human antibodies and their fragments, expressed by recombination, have shown efficacy in neutralizing snake venom toxins. Compared to animal-derived antibodies, human antibodies are less immunogenic for human receptors. Mixtures of monoclonal antibodies, targeted to neutralizing epitopes of clinically relevant toxins, have the potential to be optimized in terms of efficacy, batch-to-batch production consistency, and possibly reduced manufacturing cost (Hamza *et al.*, 2021).

REFERENCES

AMADO, Talita Ferreira *et al*. Vulnerable areas to accidents with scorpions in Brazil. **Tropical Medicine & International Health**, v. 26, n. 5, p. 591-601, 2021.

DE CASTAÑEDA, Rafael Ruiz *et al*. Snakebite and snake identification: empowering neglected communities and health-care providers with AI. **The Lancet Digital Health**, v. 1, n. 5, p. e202-e203, 2019.

DI NICOLA, Matteo R. *et al*. Vipers of Major clinical relevance in Europe: Taxonomy, venom composition, toxicology and clinical management of human bites. **Toxicology**, v. 453, p. 152724, 2021.

FORRESTER, Jared A.; WEISER, Thomas G.; FORRESTER, Joseph D. An update on fatalities due to venomous and nonvenomous animals in the United States (2008–2015). **Wilderness & Environmental Medicine**, v. 29, n. 1, p. 36-44, 2018.

GOMES, Jacimara Vasques *et al*. Perfil clínico de picadas de escorpião confirmadas em um centro de referência em Manaus, Amazônia Ocidental Brasileira. **Toxicon** , v. 187, pág. 245-254, 2020.

GREENE, Spencer C.; FOLT, Jason; WYATT, Kimberly; BRANDEHOFF, Nicklaus P. Epidemiology of fatal snakebites in the United States 1989–2018. **The American journal of emergency medicine**, v. 45, p. 309-316, 2021.

FRY, Bryan G. Snakebite: When the human touch becomes a bad touch. **Toxins**, v. 10, n. 4, p. 170, 2018.

HAMZA, Muhammad *et al*. Clinical management of snakebite envenoming: future perspectives. **Toxico**n: X, v. 11, p. 100079, 2021.

KONSTANTYNER, Thais Cláudia Roma de Oliveira *et al*. Trend in the incidence rates of accidents with venomous animals in children and adolescents in Brazil (2007–2019). **Revista Paulista de Pediatria**, v. 41, p. e2021272, 2022.

LOPES, Priscila Hess; SQUAIELLA-BAPTISTÃO, Carla Cristina; MARQUES, Mário Octávio Thá; TAMBOURGI, Denise V. Clinical aspects, diagnosis and management of Loxosceles spider envenomation: literature and case review. **Archives of toxicology**, v. 94, p. 1461-1477, 2020.

PAOLINO, Giovanni; DI NICOLA, Matteo Riccardo; AVELLA, Ignazio; MERCURI, Santo Raffaele. Venomous bites, stings and poisoning by European vertebrates as an overlooked and emerging medical problem: recognition, clinical aspects and therapeutic management. **Life**, v. 13, n. 6, p. 1228, 2023.

PUCCA, Manuela B. *et al*. Current knowledge on snake dry bites. **Toxins**, v. 12, n. 11, p. 668, 2020.

SANTANA, Luiz Alberto *et al*. Arachnidism in Brazil/Araneísmo no Brasil. **Brazilian Journal of Health Review**, v. 3, n. 5, p. 12859-12872, 2020.

TOMAZ, Valentina Ribeiro; SOARES, Marcelo Luiz Medeiros; BONFADA, Diego. Epidemiology of clinical complications of accidents caused by venomous animals in Brazil. **Revista de Epidemiologia e Controle de Infecção**, v. 13, n. 1, p. 43-52, 2023.

Chapter 18

DROWNING

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CHAPTER 18

DROWNING

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Drowning is a leading cause of death worldwide, occurring mainly in low- and middle-income countries and particularly affecting children aged 1 to 4 years due to limited control over their movements (Leavy *et al.*, 2023; Batista *et al.*, 2023). The mechanism involves water aspiration, damaging surfactant and leading to alveolar edema, resulting in a syndrome similar to acute respiratory

distress syndrome (ARDS) (Thom *et al.*, 2021). Rapid action by healthcare professionals is crucial to prevent death and neurological sequelae due to hypoxia (Batista *et al.*, 2023). Drownings rarely occur due to a single cause, making a one-size-fits-all solution unfeasible (Wallis *et al.*, 2015).

Drowning is a significant public health challenge, with over 230,000 fatal victims recorded in 2019, with 90% in underdeveloped countries, and men being twice as likely to drown compared to women due to greater exposure to aquatic activities (Leavy *et al.*, 2023). Initial management follows the drowning survival chain: prevention, recognition, flotation, water removal, and provision of appropriate care, prioritizing rescuer safety (Batista *et al.*, 2023). The scarcity of clear evidence prevents specific treatment recommendations, emphasizing the need for more research (Thom *et al.*, 2021).

In 2017, there were 295,000 unintentional drowning deaths, highlighting the urgency of standardizing care to improve outcomes (Peden; Taylor and Franklin, 2022). In prehospital care, the drowning survival chain is applied, and the victim's state of consciousness is checked, calling for technical help and initiating resuscitation when necessary (Batista *et al.*, 2023). In hospital management, assessing the airways, breathing, circulation, and temperature is fundamental, using pulse oximetry, blood pressure, body temperature, and electrocardiography monitoring, as well as laboratory tests to guide clinical conduct (Batista *et al.*, 2023).

EPIDEMIOLOGY

Drowning is one of the three leading causes of unintentional fatal injuries, with an estimated 360,000 annual deaths worldwide (Willcox-Pidgeon *et al.*, 2020). Mortality rates vary between populations due to different public health strategies and injury prevention interventions that do not always consider social, educational, cultural, and environmental determinants such as ethnicity, cultural origin, beliefs, and socioeconomic status. These determinants are interlinked in social and policy norms, influencing health outcomes and creating inequalities. High-risk populations include ethnic minorities, indigenous peoples, migrants, rural residents, and people in remote environments. Other risk factors include age, with higher prevalence in children (0-18 years), male sex, environmental context, and alcohol consumption (Willcox-Pidgeon *et al.*, 2020).

In 2019, more than 230,000 people lost their lives to drowning, with 90% of these cases occurring in low- and middle-income countries (Leavy *et al.*, 2023). Two-thirds of these deaths involved people aged 15 years or older. Risk factors for adults include alcohol consumption, swimming alone, and not wearing life jackets, as well as socio-environmental factors such as inadequate water safety skills, dangerous water conditions, and unsafe infrastructure. Globally, men have a higher risk of drowning, with a mortality rate twice that of women. This disparity is due to greater male exposure to water and involvement in riskier

activities and behaviors (Leavy *et al.*, 2015). In regions like the Eastern Mediterranean, additional factors such as migration and conflicts contribute to the high drowning rate, highlighting the need for specific interventions for these populations (Peden; Isin, 2022).

Characterized by respiratory impairment due to immersion or submersion in liquids, drowning can result in fatality or sequelae, being more prevalent in individuals with pre-existing medical conditions such as epilepsy, dementia, schizophrenia, psychotic disorders, cardiac arrhythmias, and other chronic conditions (Peden; Taylor; Franklin, 2022). These factors increase the risk of drowning, which can be accidental, intentional, or suicidal, especially in psychiatric patients. The management and prevention of drowning require a comprehensive approach, considering all these factors. The prevalence of drowning is high in pediatric patients, being the leading preventable cause of death in children aged 1 to 4 years, with severe neurological sequelae in 5 to 10% of surviving victims (Batista *et al.*, 2023). The prognosis depends on the interval between submersion and rescue, with better outcomes when rescue occurs in less than six minutes (Batista *et al.*, 2023).

Risk factors for drowning include intrinsic elements such as male sex, age 0 to 4 years, adolescents, history of neurological disorders, and cardiomyopathies, and extrinsic factors such as alcohol and drug consumption, low education, rural residence, lack of pool fencing, and lack of swimming equipment. Factors associated with worse outcomes include age under 5 years, submersion time over five minutes, higher Szpilman score, lower Glasgow coma scale on admission, water temperature (cold), hypothermia below 30°C, acidosis, hyperglycemia, hypernatremia, hyperkalemia, elevated lactate and liver enzymes, delay in starting cardiopulmonary resuscitation (CPR) or duration over 30 minutes, and abnormal chest x-ray (Batista *et al.*, 2023). Understanding these risk factors is essential to implementing effective preventive strategies. For example, constant supervision of young children, swimming instruction, and the implementation of fences around water bodies can significantly reduce childhood drowning rates (Tyler *et all.*, 2017).

DIAGNOSIS

When water comes into contact with the airways, protective reflexes such as coughing and laryngospasm occur, leading to hypoxia. Hypoxia results in the relaxation of the respiratory muscles, ceasing laryngospasm and allowing more water to be aspirated into the lungs. This causes mild acidosis, apnea, loss of consciousness, cerebral hypoxia, and arrhythmias. Simultaneously, cytokine release, alveolar-capillary membrane integrity disruption, and intense pulmonary edema occur (Batista *et al.*, 2023).

In the cardiovascular system, initially, there is tachycardia, followed by a reduction in heartbeats, pulmonary hypertension, and decreased cardiac output (Cibulski *et al.*, 2023). Pulseless electrical activity sets in, evolving to cardiac arrest due to asystole. Water temperature can influence the progression time of these events; in cases of rapid hypothermia, the evolution to asystole can last up to an hour (Cibulski *et al.*, 2023).

In drowning emergencies, resuscitation must be initiated immediately, and the victim must be transported directly to an emergency service. The goal is to restore effective circulation, including respiratory support, pulse oximetry, electrocardiography, blood pressure, and body temperature measurement. Management depends on the severity and risk of death, potentially including oxygen administration via nasal catheter, face mask, or non-invasive ventilation (NIV). In more severe cases, mechanical ventilation (MV) is considered (Batista *et al.*, 2023).

If there is no pulse, continuous chest compressions are necessary. In cases of poor perfusion, supplementary volume such as crystalloids or blood can be administered, and vasoactive drugs like dobutamine may be used in pediatric patients. Clinical, laboratory, and echocardiographic evaluation is essential, including a complete blood count, electrolytes, glucose, arterial blood gas analysis, renal function, liver enzymes, and chest x-ray. Antibiotics are generally not indicated unless there is suspicion of water contamination, which can cause fatal pneumonia. In such situations, broad-spectrum antibiotics are considered. Diuretics may be indicated in case of hypervolemia or reduced urine output after volume restoration (Batista *et al.*, 2023).

It is crucial to monitor oxygen saturation (at least 90%) for 6 to 24 hours to prevent hypothermia. In cases of apnea, tracheostomy and intubation are recommended. Children are more prone to hypothermia due to the body mass-to-surface ratio, requiring specific warming care. Mild hypothermia (32-35°C) can be treated with passive rewarming using blankets or thermal blankets, while moderate cases (28-32°C) may require heated oxygen and warmed intravenous infusions, with strict monitoring to avoid rewarming shock. Severe hypothermia (<28°C) requires active internal warming measures with saline lavage and external forced-air warming. If there are signs of shock, intravenous or intraosseous saline solution can be administered, and inotropes may be necessary in case of cardiac dysfunction (Cibulski *et al.*, 2023).

TREATMENT

Effective treatment of drowning is essential to improve survival rates and minimize long-term sequelae. Typical interventions include cardiopulmonary resuscitation (CPR), adequate ventilation and oxygenation, advanced life support, and body temperature control, each applied as per clinical need (Leavy *et al.*, 2023; Wallis *et al.*, 2015; Sampaio *et al.*, 2022).

Cardiopulmonary resuscitation (CPR) is the initial and most vital intervention in drowning treatment, to be initiated as quickly as possible to restore blood circulation and breathing. Research indicates that CPR performed by bystanders can significantly increase survival chances, especially when followed by advanced medical care in a hospital. Early application of CPR is widely recognized as an essential life-saving measure (Leavy *et al.*, 2023; Wallis *et al.*, 2015).

Adequate ventilation and oxygenation are fundamental to prevent hypoxia and brain damage, often requiring the use of mechanical ventilators and other respiratory support devices. In severe cases, mechanical ventilation may be necessary to maintain adequate oxygenation levels until spontaneous respiratory function is restored. Studies indicate that effective ventilation is crucial to improving outcomes in patients who suffered severe drowning (Sampaio *et al.*, 2022). For patients with spontaneous breathing, oxygen can be administered via nasal catheter, face mask, or non-invasive ventilation (NIV). However, for those with a Glasgow coma scale (GCS) score below 8, apnea, or progressive respiratory distress, invasive mechanical ventilation (MV) should be considered, offering intermittent positive-pressure oxygen or positive end-expiratory pressure. High concentrations of oxygen should be provided to achieve a saturation above 92%. Protective ventilation is recommended, with tidal volume between 4-6 mL/kg and plateau pressure below 30 cmH_2O. The goal is to maintain PaO_2 between 55 and 80 mmHg and reduce FiO_2 as quickly as possible to avoid lung injury caused by hyperoxia (Batista *et al.*, 2023).

Advanced life support, including the use of vasopressor medications and continuous monitoring, is vital to stabilize severe patients and prevent multiple organ failure. In many cases, hemodynamic support is necessary to maintain adequate perfusion of vital organs. The implementation of advanced life support protocols has been shown to significantly improve survival rates and clinical outcomes in critical patients (Leavy *et al.*, 2023).

Body temperature control is a crucial aspect of drowning treatment, especially in victims exposed to cold waters. Gradual and controlled body temperature recovery helps prevent additional complications such as cardiac arrhythmias. Proper hypothermia management, using passive or active warming techniques, is essential to ensure the patient's hemodynamic and neurological stability. Additionally, monitoring and treating pulmonary complications, such as acute respiratory distress syndrome (ARDS), are essential for the patient's full recovery (Wallis *et al.*, 2015; Sampaio *et al.*, 2022).

Clinical evaluation should guide the request for laboratory and imaging tests. It is recommended to request a complete blood count, electrolytes, glucose, arterial blood gas analysis, renal function, liver enzymes, and chest x-ray (CXR). As evidenced in the current literature, worse outcomes are associated with low pH, bicarbonate alteration, hypernatremia, hyperkalemia, acute kidney injury, elevated lactate, glucose, and liver enzymes. Cervical spine x-rays may be indicated if cervical injury is suspected, as well as other complementary tests depending on the clinical picture (Batista *et al.*, 2023).

The management of drowning has evolved significantly with the introduction of new treatment modalities and emerging tools. Among the most promising interventions are advanced resuscitation techniques, innovative technologies for monitoring and life support, and emerging pharmacological approaches aimed at improving patients' clinical outcomes. These innovations are increasingly being incorporated into treatment protocols to provide a more effective response to drowning incidents (Wallis *et al.*, 2015).

One of the most notable advances is the use of innovative ventilation devices and advanced respiratory support techniques. New non-invasive ventilation modalities are being explored to optimize oxygenation and carbon dioxide removal in drowning patients. These techniques aim to reduce the risk of complications associated with invasive ventilation, such as ventilator-induced lung injury, and improve clinical outcomes for patients (Leavy *et al.*, 2023; Wallis *et al.*, 2015).

Emerging technologies such as advanced sensors and artificial intelligence for continuous vital signs monitoring are revolutionizing drowning management. These devices enable early detection of clinical deterioration, facilitating rapid and targeted interventions. Remote monitoring systems are also being implemented to follow patients during the recovery phase, ensuring any complications are promptly identified and treated (Leavy *et al.*, 2023; Wallis *et al.*, 2015).

Emerging pharmacology is also playing a crucial role in drowning treatment. New pharmacological agents, such as inflammatory response modulators, are being investigated to reduce damage caused by hypoxia and systemic inflammation that often accompany drowning. The administration of medications like corticosteroids and antioxidants has shown potential to improve neurological recovery and reduce the risk of long-term sequelae (Leavy *et al.*, 2023; Sampaio *et al.*, 2022).

Extracorporeal membrane oxygenation (ECMO) is an important resuscitation tool for the hypothermic drowning victim. The treatment focuses on rewarming and oxygenation, in addition to providing circulation. ECMO can be delivered in veno-venous or veno-arterial modalities. The veno-venous type is useful for patients who have regained a perfusing heart rhythm but cannot perform gas exchange due to alveolitis, pulmonary edema, or surfactant deactivation induced by aspiration. The veno-arterial ECMO is considered for patients without a perfusing heart rhythm, thus providing circulatory support. Besides providing rewarming, oxygenation, and circulation, ECMO can also correct metabolic alterations. Providing circulatory support is critical because over 90% of patients with severe hypothermia experience cardiac arrest. Rewarming causes the heart rhythm to transition from asystole to ventricular fibrillation before returning to sinus rhythm, and ECMO maintains hemodynamic stability and circulatory support during this transition (Bauman *et al.*, 2021).

Despite the benefits of ECMO, mortality remains high. In drownings with hypothermia and cardiorespiratory arrest, there is an inherent risk of severe neurological damage in survivors, which some patients may consider worse than death. Other obstacles include low availability and high cost, in addition to the need for specialized professionals. However, ECMO is a lifesaving therapy in drowning cases (Bauman *et al.*, 2021).

Evaluating the effectiveness and safety of these emerging treatments is crucial for their incorporation into clinical protocols. Rigorous clinical studies and systematic reviews are needed to validate the benefits of these new approaches. The existing literature suggests that, although promising, these innovations should be implemented with caution

and accompanied by continuous monitoring to ensure patient safety. The integration of new technologies and treatments should be done gradually, based on solid evidence and well-established clinical practices (Leavy *et al*., 2023; Wallis *et al*., 2015; Sampaio *et al*., 2022).

Drowning treatment presents several significant challenges that can negatively impact the effectiveness of interventions and patient recovery. One of the main challenges is the variability in the circumstances of each drowning incident, which requires personalized and rapid approaches to treatment. Additionally, the availability and adequacy of emergency resources at the incident site are crucial for first aid and can determine the patient's survival. This variability complicates the standardization of treatment protocols, which can lead to critical delays in the administration of essential care (Wallis *et al*., 2015).

Another important challenge is the lack of adequate and continuous training of healthcare professionals and rescuers in advanced resuscitation techniques and drowning management. Studies show that bystander-performed cardiopulmonary resuscitation (CPR) is effective, but often first responders may not be adequately trained and updated on best practices for CPR and other critical interventions. The lack of training can result in an inadequate response during the crucial first minutes after drowning, reducing survival chances and increasing the risk of neurological sequelae (Leavy *et al*., 2023; Sampaio *et al*., 2022).

Additionally, integrating new technologies and emerging treatments into drowning management faces significant barriers. Although continuous monitoring technologies and artificial intelligence have the potential to improve early detection of clinical deterioration, implementing these systems can be complex and expensive. The lack of adequate infrastructure and financial resources in many areas, especially in low-income regions, prevents the widespread adoption of these innovations, limiting potential benefits for patients (Sampaio *et al*., 2022).

To overcome these challenges, several strategies can be adopted. Implementing continuous training and refresher programs for healthcare professionals and rescuers is essential to ensure they are up to date with best practices and advanced resuscitation techniques. Additionally, creating standardized protocols that can be quickly adapted to the specific circumstances of each drowning incident can improve the initial response and treatment outcomes. Collaboration between governments, health institutions, and communities to fund and implement emerging technologies, as well as promoting awareness campaigns on the importance of drowning prevention and first aid training, is crucial to improving the effectiveness of drowning treatment (Leavy *et al*., 2023; Sampaio *et al*., 2022).

Although it is a frequent cause of death, drowning often does not result in hospitalization and is frequently underreported. This represents a significant challenge due to the scarcity of evidence, limited investigation, lack of data to guide the effective implementation of its treatment - especially concerning the duration of care and the need for hospital or intensive care unit (ICU) admission. Even less severe incidents should be reported to improve the availability of data and information that can benefit the quality of subsequent studies (Thom *et al*., 2021; Cibulski *et al*., 2023).

PREVENTION

The American Academy of Pediatrics advises that all children over 4 years old, who do not have motor development delays, receive swimming lessons. For children under 4 years old, it is not recommended due to the association with increased respiratory infections and life risk. However, it is important to remember that water skills alone do not prevent drownings, making measures such as pool fences and constant adult supervision indispensable. Proper child supervision is essential to prevent submersion accidents and should be complemented by community strategies (Batista *et al*., 2023; Capela *et al*., 2023).

In a study conducted by Capela *et al*. (2023), only 12% of reported incidents had a lifeguard present, which can largely be attributed to accidents occurring in private pools in condominiums, hotels, or private residences. To address this issue, preventive measures can be adopted, such as installing barriers to limit access to water, proper use of flotation devices for children (such as armbands and life jackets), implementing swimming lessons and water safety education in school curricula, teaching safe practices in aquatic environments, training residents and tourists in self-rescue techniques, and providing basic life support (BLS) to the general community.

In primary care, the family health team plays a role in risk detection through home visits, paying individual attention to each family and thus proposing safety measures to prevent accidents involving children in domestic environments, as these accidents are often associated with death. Another measure is community education, as studies have shown that mothers lack adequate knowledge on how to prevent this type of accident (Sampaio *et al*., 2022).

REFERENCES

BATISTA, Lorena Luana, *et al.* Acidentes por submersão em pediatria: Revisão de literatura. **Residência Pediátrica**, 2023.

BAUMAN, Brent D., *et al.* Treatment of hypothermic cardiac arrest in the pediatric drowning victim, a case report, and systematic review. **Pediatric emergency care**, v. 37, n. 10, p. e653-e659, 2021.

CAPELA, Joana Brígida, *et al.* Analysis of submersion accidents at a level II hospital and literature review. **Pediatric oncall journal**, v. 21, n. 3, 2023.

CIBULSKI, Gabriela Mazzurana, *et al.* Intervenções e técnicas de suporte à vida nos afogamentos: uma revisão narrativa. **Brazilian Journal of Health Review**, v. 6, n. 1, p. 468-478, 2023.

LEAVY, Justine E., *et al.* A review of interventions for drowning prevention among adults. **Journal of community health**, v. 48, n. 3, p. 539-556, 2023.

LEAVY, Justine E., *et al.* Recreational drowning prevention interventions for adults, 1990–2012: a review. **Journal of community health**, v. 40, p. 725-735, 2015.

PEDEN, Amy E.; IŞIN, Ali. Drowning in the Eastern Mediterranean region: a systematic literature review of the epidemiology, risk factors and strategies for prevention. **BMC public health**, v. 22, n. 1, p. 1477, 2022.

PEDEN, Amy E.; TAYLOR, Danielle H.; FRANKLIN, Richard C. Pre-existing medical conditions: a systematic literature review of a silent contributor to adult drowning. **International journal of environmental research and public health**, v. 19, n. 14, p. 8863, 2022.

SAMPAIO, Hellen dos Santos; RIBEIRO, Juliane Portella; TAVARES, Amanda do Rosário; RODRIGUES, Matheus dos Santos. Acidentes em crianças menores de um ano e ações preventivas: revisão integrativa. **Enfermagem na Promoção e Prevenção da Saúde**, Vol. 1, 2022.

THOM, Ogilvie, *et al.* Treatment of the lung injury of drowning: a systematic review. **Critical Care**, v. 25, p. 1-11, 2021.

TYLER, Matthew D., *et al.* The epidemiology of drowning in low-and middle-income countries: a systematic review. **BMC public health**, v. 17, p. 1-7, 2017.

WALLIS, Belinda A., *et al.* Interventions associated with drowning prevention in children and adolescents: systematic literature review. **Injury prevention**, v. 21, n. 3, p. 195-204, 2015.

WILLCOX-PIDGEON, Stacey M.; FRANKLIN, Richard Charles; LEGGAT, Peter A; DEVINE, Sue. Identifying a gap in drowning prevention: high-risk populations. **Injury prevention**, v. 26, n. 3, p. 279-288, 2020.

Chapter 19

MANAGEMENT OF DIFFICULT AIRWAY IN THE TRAUMATIZED PATIENT

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CHAPTER 19

MANAGEMENT OF DIFFICULT AIRWAY IN THE TRAUMATIZED PATIENT

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Airway management is a crucial aspect in the treatment of critically ill patients, especially in trauma situations, serving as a cornerstone for emergency medical care (Jarvis et al., 2023). The need for rapid and effective interventions can mean the difference between life and

death. In this context, understanding the complications and best practices in managing difficult airways is fundamental to improving clinical outcomes. Traumas, especially those involving the head, neck, and chest, can lead to complications in maintaining a patent airway, which is essential for adequate ventilation and oxygenation of the patient. In traumatized patients, the importance of correcting hypoxemia and hypotension to reduce morbidity and mortality is emphasized (Jain *et al*., 2016). The combination of hypoxemia and hypotension is additive, with an adjusted probability of death twice as high as the increase in mortality associated with either event alone (Spaite *et al*., 2017). It is noteworthy that difficulty in airway management can be unpredictable and influenced by anatomical and physiological factors (Kovacs; Sowers, 2018).

There is controversy about the effectiveness of early airway management in trauma, presenting conflicting evidence about the benefits and risks of prehospital endotracheal intubation. Therefore, it is necessary to consider the specific context of each patient, the skills of the medical team, and the ability to anticipate and respond to complications (Jain et al., 2016). If oxygenation and ventilation can be maintained, prehospital establishment of a definitive airway may not be necessary and sometimes detrimental (Hussmann *et al*., 2011). A non-critical airway intervention should not delay transport to the hospital. However, if travel time is long, definitive airway management may be performed as soon as indicated (Kummer *et al*., 2007). The Advanced Trauma Life Support Manual advocates three underlying concepts: (1) treat the greatest threat to life first, (2) lack of a definitive diagnosis should never impede the application of an indicated treatment, and (3) a detailed history is not essential to begin the evaluation of a patient with acute injuries.

Emergency airway management in critically ill patients, whether in the field or the Emergency Department (ED), is often associated with adverse events and complications such as hypoxemia, esophageal intubation, and hypotension. Inadequate oxygenation and ventilation can lead to unfavorable outcomes, making airway management a priority in the resuscitation of these patients (Bernhard *et al*., 2019). Given the above, it is worth emphasizing the importance of prehospital airway management nowadays, so that ventilation with just a BVM (bag-valve-mask) or ETI (endotracheal intubation) can be used in airway management in adult trauma patients, recognizing that the goal is to optimize oxygenation and ventilation, avoiding hypoxia, hypotension, and hyperventilation (Jarvis *et al*, 2023).

In recent years, there have been significant advances in the techniques and devices used for difficult airway management, including the introduction of videolaryngoscopes and supraglottic devices. The concept of a difficult airway is not limited to anatomical difficulties but also includes factors such as the presence of blood, secretions, or vomit that can obstruct visualization and make intubation difficult. Updates in guidelines emphasize the importance of adequate preparation, continuous training, and the use of structured algorithms to guide clinical decisions in trauma situations. Additionally, interprofessional collaboration and the use of realistic simulations have proven effective in preparing emergency teams for

these complex challenges. Current guidelines also highlight the importance of continuous evaluation and adaptation of management strategies based on patient responses and the specific circumstances of the trauma (Hall *et al*, 2023).

The prevalence of airway management in emergencies is significant, with studies showing that success in the first intubation attempt is directly related to a reduction in complications (Bernhard *et al.*, 2019). Furthermore, airway obstruction was the second most common cause of potentially preventable death in all combat casualties in the US from October 2001 to June 2011 (Kovacs; Sowers, 2018). The incidence of difficult airway in trauma patients varies widely depending on the type and severity of the trauma, as well as the care environment. Studies indicate that up to 20% of traumatized patients may present some degree of difficulty in airway management (Hall *et al*, 2023). Craniofacial traumas, cervical injuries, and thoracic injuries are often associated with an increased incidence of difficult airway. Mortality associated with failures in airway management can be high, highlighting the need for effective management strategies. Epidemiological data also suggest that the presence of a difficult airway is correlated with a significant increase in prehospital care time and the risk of in-hospital complications. Early recognition and appropriate intervention are crucial to mitigating these risks (Hall *et al.*, 2023).

Identifying a difficult airway is essential for effective management, using parameters such as the LEMON law and the Cormack/Lehane classification (Bernhard *et al*, 2019). In the context of trauma, rapid and systematic patient evaluation includes visual inspection of deformities and assessment of the level of consciousness. Tools like the modified Mallampati scale and the 3-3-2 rule are useful, but trauma requires flexibility and clinical judgment. Radiological imaging and portable devices like ultrasounds improve diagnostic accuracy and emergency decision-making. Collaboration with specialists, such as anesthesiologists, may be necessary in complex cases. Additional complications, such as hematomas and facial fractures, make the evaluation more complex, and advanced imaging methods and techniques like videolaryngoscopy are particularly useful (Hall *et al.*, 2023).

Airway management can be performed in both prehospital and hospital settings. In prehospital care, 52.4% of patients were treated by Emergency Medical Services (EMS) with techniques such as endotracheal intubation and supraglottic devices (SAD). In the hospital, 47.6% were managed by the emergency department team using direct laryngoscopy, videolaryngoscopy, SADs, cricothyroidotomy, and tracheostomy (Bernhard *et al.*, 2019). Endotracheal intubation is preferred for its efficacy, but SADs, such as laryngeal masks, are alternatives in cases of intubation failure. Videolaryngoscopy improves vocal cord visualization, increasing success rates and reducing complications (Bernhard *et al.*, 2019).

Managing the difficult airway in trauma requires a stepwise approach, starting with less invasive techniques and progressing to more invasive interventions as necessary. In extreme situations, surgical cricothyroidotomy may be necessary, being a last resort

that requires significant technical skill. Percutaneous cricothyroidotomy is a less invasive alternative in some cases (Hall *et al*., 2023). Current trends in managing the difficult airway focus on minimizing intubation attempts to reduce complications, with success on the first attempt being crucial (Bernhard *et al*., 2019). The use of videolaryngoscopy is becoming more common, improving airway visualization and increasing success rates, while reducing trauma and complications (Bernhard *et al*., 2019). Emphasis on interprofessional training and the use of realistic simulations is highlighted to prepare care teams. The development of new devices and techniques aims to increase safety and efficacy, with customized algorithms for each trauma scenario and the use of artificial intelligence to predict difficulties and suggest interventions in real-time (Hall *et al*., 2023). Studies highlight the need for improved practices and well-defined protocols to reduce complications and improve clinical outcomes. Establishing a national airway registry can continuously improve outcomes in emergency airway management (Bernhard *et al*., 2019).

EPIDEMIOLOGY

Epidemiological data on the management of difficult airways in trauma reveal the importance and frequency of this challenge in emergency settings. The mortality associated with failures in airway management is significant, emphasizing the need for rapid and effective interventions. Data also show that the use of advanced techniques, such as videolaryngoscopy, has increased, improving success rates in intubation in difficult cases. Continuous education and simulation training for healthcare professionals are identified as critical factors for improving outcomes in these cases (Nakao *et al*., 2015). Additionally, the baseline characteristics and primary indications in patients requiring airway management due to trauma include an average age of 56 years, with two-thirds of the patients being male. The primary reason was traumatic cardiac arrest, which prompted intubation in 32.6% of all traumatized patients, while traumatic brain injury accounted for 30.4% (Nakao *et al*., 2015). Furthermore, rapid sequence intubation (RSI) is the initial method of emergency airway management in most trauma patients, chosen in 23.9% of all trauma patients and 35.5% of patients without cardiac arrest. Cricothyroidotomy was performed as the initial airway management strategy in 2.2% of all trauma patients and 0.4% of patients without cardiac arrest. Direct laryngoscopy was used in most intubations (90.5%), with the remaining performed using videolaryngoscopy (4.1%), bronchoscopy (2.4%), or lighted stylet (0.1%) on the first attempt (Nakao *et al*., 2015).

Emergency medicine (EM) physicians are primarily responsible for intubations in 81% of the surveyed institutions. In trauma wards, EM physicians were responsible for 61.4% of intubations. Thus, EM physicians were solely responsible for intubations in the emergency department in 81% of the surveyed institutions, while members of the anesthesiology and trauma surgery departments were responsible in 6.7% and 1.7% of

the institutions, respectively (Chiaghana *et al*., 2019). In the trauma area, EM physicians are the primary providers of airway intubation in 61.4% of the institutions, while members of the anesthesiology and trauma surgery departments occupied the second and third places (20% and 6.8%, respectively). This was a much higher percentage of care provided by anesthesiologists and surgeons in trauma wards compared to EDs. The EM and anesthesiology departments were considered managers in 7.7% of the institutions, while the emergency and trauma surgery departments were the primary intubation team in 1.8% of the institutions (Chiaghana *et al*., 2019).

MANAGEMENT

Successful airway management is crucial in emergency medicine, being one of the main survival factors in trauma patients (Lentz *et al*., 2020). Rapid identification and intervention are essential to prevent organ decompensation, requiring a careful and flexible plan (Estime; Kuza, 2019; Lentz *et al*., 2020). In trauma, the initial therapeutic approach consists of a broad assessment of mortality predictors, such as hypoxemia, upper airway obstruction, level of consciousness, and hemodynamic instability, using mnemonics like ROMAN and LEMON to predict difficult airways (Estime; Kuza, 2019).

Clinical assessment should precede airway management, being thorough in elective contexts or abbreviated in emergencies to avoid injuries secondary to tracheal intubation (Goto *et al*., 2019). After clinical judgment, the patient should be prepared, explaining the procedure and obtaining consent, and verifying the necessary equipment and materials for intubation. Optimal patient positioning, such as the «Sniffing» or «Ramp» position, is fundamental for better glottic visualization, especially in patients with cervical trauma or morbid obesity (Brown III *et al*., 2020).

Hemodynamic monitoring and oximetry are essential during intubation, with capnography ensuring the correct placement of the tracheal tube. Pre-oxygenation is mandatory, performed with a face mask and 100% oxygen for 4 to 6 minutes before anesthesia, especially benefiting obese and pregnant patients due to the reduction of functional residual capacity (FRC). General anesthesia precedes laryngoscopy, using analgesic, hypnotic, and neuromuscular blocking drugs, individualized for each clinical context (Goto *et al*., 2019).

The classic orotracheal intubation technique is performed with laryngoscopy or videolaryngoscopy, introducing the blade at the patient›s right labial commissure until visualization of the vocal cords. Videolaryngoscopy associated with the bougie is especially useful in managing difficult airways, such as in cervical trauma and morbidly obese patients (Brown III *et al*., 2020). Prehospital intubation (PI) is more common in patients with severe head injuries (GCS $\leq$ 8). Most prehospital PIs were performed without medications, while most PIs in the emergency department (ED) used medications (Renberg *et al*., 2023). The

overall first-pass success (FPS) intubation rate in emergency departments is 84.1%, with regional variations and types of intubations (Park *et al*., 2016). Trauma-related intubations have a lower FPS rate (81.8%) due to the inherent complexities and challenges of these cases, such as anatomical interruptions and unexpected airway obstructions.

In the USA, the overall success rate of advanced airway management (AAM) is 89.1%, with variations according to the technique used, such as conventional endotracheal intubation (cETI) with 76.9% success and neuromuscular blockade-assisted intubation (NMBA-ETI) with 89.7%. The practice of rapid sequence intubation (RSI) varies significantly across continents: in Asia, the proportion of intubations performed by RSI is relatively low (21.4% to 49.6%) compared to higher rates in Europe, North America, and Australia (73.0% to 85.0%). These variations suggest that demographic and geographic factors significantly influence intubation practices and success rates (Nwanne *et al*., 2020).

Emergent cricothyrotomy (EC) is a critical procedure used as a last resort when other airway management techniques fail or are inadvisable. It is most commonly necessary in patients with severe maxillofacial injuries, oropharyngeal obstructions, or those who cannot be intubated by standard methods. The procedure is rare, with published data on its incidence being scarce. However, it is estimated that EC occurs in nearly 1-3% of trauma treatment cases, 0.4% in non-traumatic emergency conditions, and 0.003% in operating room scenarios (George *et al*., 2022). EC is associated with significant risks, including bleeding, infection, and injury to nearby anatomical structures. These complications can lead to long-term problems, such as laryngeal scarring or stenosis, which can affect speech and breathing. A meta-analysis found a 3.9% rate of laryngotracheal sequelae requiring additional intervention, with chronic subglottic stenosis occurring at a rate of 1.7%. The study conducted at Arrowhead Regional Medical Center over a decade identified that only 0.17% of patients required EC, highlighting its rarity even in a trauma center (George *et al*., 2022).

There has also been a significant increase in the use of supraglottic airways (SGA) over the studied period, with a statistically significant trend, although the success rates of intubation and SGA insertion have not changed significantly (Nwanne *et al*., 2019).

Upper airway ultrasound is an emerging and valuable tool, being non-invasive, simple, and portable (Osman; Sum, 2016). It allows the identification of important anatomies and the prediction of airway size and endotracheal tube size. Studies show that ultrasound can accurately predict endotracheal tube size and anticipate difficult intubations (Osman; Sum, 2016). Videolaryngoscopy is establishing itself as the first-line technique in managing upper airways in emergencies, providing better glottic visualization and greater first-attempt intubation success, reducing peri-intubation adverse events (Brown III *et al*., 2020). In cervical spine injuries, videolaryngoscopy minimizes neck movements, reducing the risk of secondary neurological injury (Coppola *et al*., 2015). Managing difficult airways in trauma is challenging due to the unpredictable and potentially severe nature of injuries, such as

fractures, hemorrhages, and edema that hinder airway visualization and manipulation. Significant hemorrhages and vomiting obstruct vision during laryngoscopy and increase the risk of aspiration (George *et al*., 2022).

Patients with suspected cervical spine injury should be immobilized, limiting head and neck manipulation during intubation, increasing the difficulty of airway management. Efficient airway management is crucial in emergency medicine, with proper identification and understanding of the underlying physiology, careful preparation, and post-intubation management being fundamental (Lentz *et al*., 2020).

Adverse events during airway management in emergencies are common, including post-intubation cardiac arrest. Many of these events can be avoided with proper identification and careful management. Patients with high-risk characteristics, such as trauma and morbid obesity, should be managed by experienced airway professionals (Lentz *et al*., 2020).

REFERENCES

BERNHARD, Michael, et al. Airway Management in the Emergency Department (The OcEAN-Study)-a prospective single centre observational cohort study. **Scandinavian journal of trauma, resuscitation and emergency medicine**, v. 27, p. 1-9, 2019.

BROWN III, Calvin A., *et al*. Video laryngoscopy compared to augmented direct laryngoscopy in adult emergency department tracheal intubations: a National Emergency Airway Registry (NEAR) study. **Academic Emergency Medicine**, v. 27, n. 2, p. 100-108, 2020.

CHIAGHANA, Chukwudi, *et al*. Emergency department airway management responsibilities in the United States. **Anesthesia & Analgesia**, v. 128, n. 2, p. 296-301, 2019.

COPPOLA, S., *et al*. Maxillofacial trauma in the emergency department: pearls and pitfalls in airway management. **Minerva Anestesiologica**, v. 81, n. 12, p. 1346-1358, 2015.

ESTIME, Stephen R.; KUZA, Catherine M. Trauma airway management: induction agents, rapid versus slower sequence intubations, and special considerations. **Anesthesiology Clinics**, v. 37, n. 1, p. 33-50, 2019.

GEORGE, Nicholas, *et al*. Comparison of emergency airway management techniques in the performance of emergent Cricothyrotomy. **International Journal of Emergency Medicine**, v. 15, n. 1, p. 24, 2022.

GOTO, Tadahiro, *et al.* Advancing emergency airway management practice and research. **Acute Medicine & Surgery**, v. 6, n. 4, p. 336-351, 2019.

HALL, Thomas, *et al.* Emergency airway management in a tertiary trauma centre (AIRMAN): a one-year prospective longitudinal study. **Canadian Journal of Anesthesia/Journal canadien d›anesthésie**, v. 70, n. 3, p. 351-358, 2023.

JAIN, Uday, *et al*. Management of the traumatized airway. **Anesthesiology**, v. 124, n. 1, p. 199-206, 2016.

JARVIS, Jeffrey L., *et al.* Evidence-based guideline for prehospital airway management. **Prehospital Emergency Care**, v. 28, n. 4, p. 545-557, 2023.

KOVACS, George; SOWERS, Nicholas. Airway management in trauma. **Emergency Medicine Clinics**, v. 36, n. 1, p. 61-84, 2018.

LENTZ, Skyler, *et al.* High-risk airway management in the emergency department: diseases and approaches, Part II. **The Journal of Emergency Medicine**, v. 59, n. 4, p. 573-585, 2020.

NAKAO, Shunichiro, *et al.* Trauma airway management in emergency departments: a multicentre, prospective, observational study in Japan. **BMJ open**, v. 5, n. 2, p. e006623, 2015.

NWANNE, Tracy, *et al*. Advanced airway management success rates in a national cohort of emergency medical services agencies. **Resuscitation**, v. 146, p. 43-49, 2020.

OSMAN, Adi; SUM, Kok Meng. Role of upper airway ultrasound in airway management. **Journal of intensive care**, v. 4, n. 1, p. 52, 2016.

PARK, Louise; ZENG, Irene; BRAINARD, Andrew. Systematic review and meta-analysis of first-pass success rates in emergency department intubation: creating a benchmark for emergency airway care. **Emergency Medicine Australasia**, v. 29, n. 1, p. 40-47, 2017.

RENBERG, Mattias, *et al.* Prehospital and emergency department airway management of severe penetrating trauma in Sweden during the past decade. **Scandinavian journal of trauma, resuscitation and emergency medicine**, v. 31, n. 1, p. 85, 2023.

Chapter 20

DEEP VEIN THROMBOSIS

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CHAPTER 20

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Deep vein thrombosis (DVT) is characterized by the abnormal formation of blood clots in deep veins, resulting in constriction, obstruction, and collateral venous return. These clots can cause swelling, pain, ulceration, necrosis, disability, and, in severe cases, pulmonary embolism (PE), which can be fatal. The

incidence of DVT increases the risk of PE, making venous thromboembolism (VTE) a common cause of hospital death, affecting around 10 million people globally. Women between 20 and 40 years are at higher risk due to reproductive factors, while men are at higher risk in other age groups (Khan et al., 2021; Jiang et al., 2024).

In the United States, it is estimated that DVT affects up to 600,000 individuals annually, resulting in 100,000 to 180,000 deaths from VTE. DVT is considered a medical emergency requiring immediate attention (Brill, 2021). Upper extremity deep vein thrombosis (UEDVT) accounts for about 6% of DVT cases, being less common than lower extremity deep vein thrombosis (LEDVT) (Khan; Marmaro; Cohen, 2021).

Three main factors contribute to DVT formation: static blood flow, venous wall damage, and hypercoagulability. Recent studies have shown that neutrophil extracellular traps (NETs) are closely related to DVT (Yao et al., 2023). In diagnosis, color Doppler ultrasound has become essential due to its high sensitivity and accuracy. Diagnostic tests include sequential clinical evaluations and the D-dimer test, which, despite its moderate sensitivity, is complementary in diagnosis (Jiang et al., 2024).

For patients with intermediate to high-risk PE and signs of hemodynamic decompensation, thrombolytic therapy should be considered. DVT treatment is based on immediate anticoagulation, whose failure can worsen the disease (Yao et al., 2023). Pharmacological studies have shown that heparin, besides its preventive effect against DVT, reduces the expression of ITAM1, ITGAM, and fibronectin in thrombus tissue, which are critical in mediating platelet adhesion and binding (Li et al., 2020). The optimization of screening to assess the risk of venous thromboembolism (OPTIMEV) has provided relevant data for the treatment of isolated distal DVT of the lower limbs (Galanaud et al., 2023).

In diagnosis, several biomarkers, such as microRNA, interleukin-1, interleukin-8, and other inflammatory markers, have been investigated as predictive tools for DVT. However, no identified substance is sufficiently sensitive or specific to predict DVT diagnosis. Metabolomics, which studies the types and amounts of endogenous metabolites and their changes in response to external disturbances, is a promising approach to better understand the pathophysiology of DVT, identify biomarkers, and help develop accurate clinical diagnosis (Jiang et al., 2024).

As recurrent DVT is a significant risk factor for post-thrombotic syndrome (PTS), proper anticoagulation management remains a challenge. Although no specific anti-inflammatory effect has been reported for DOACs, these drugs target two coagulation factors with pro-inflammatory properties. Recent studies show that dabigatran may have anti-inflammatory effects, while the use of direct oral FXa inhibitors, such as rivaroxaban, significantly reduces PTS. Patients treated with rivaroxaban for six months had better outcomes compared to those treated with conventional therapy overlapped with low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKA) (Borgel et al., 2019).

EPIDEMIOLOGY

VTE, which includes DVT and PE, is a frequently underestimated vascular condition. In Western regions, approximately 1 in 12 individuals will be diagnosed with VTE during their lifetime, with an incidence rate of about 1-2 per 1,000 person-years in Europe and the USA. In contrast, rates are lower in Asia, such as in South Korea, where the incidence is 0.2 per 1,000 person-years. In the USA, it is estimated that there are approximately 1,220,000 annual cases of VTE, with about 370,000 cases of PE and 857,000 cases of DVT (Lutsey and Zakai, 2023).

Risk factors for VTE include obesity, lack of physical exercise, adverse social conditions, and missed prevention opportunities during hospitalization. In patients with incurable cancer, VTE is treated with anticoagulants indefinitely, while hormone-associated VTE in women receives limited treatment. Surgery and bone fractures are established risk factors for VTE. The postoperative risk varies with the type of surgery and is influenced by factors such as advanced age, male sex, obesity, active cancer, malnutrition, pneumonia, blood transfusions, and myocardial infarction (Lutsey and Zakai, 2023). Long bone fractures of the leg, trauma-related fractures, and surgically treated fractures pose a higher risk for VTE.

Between 40% and 60% of all VTE events occur during or within three months after hospitalization, increasing the risk by approximately 100 times. Hospitalization for infection in the past 30 days increases the risk of VTE by 2.7 times, while antibiotic treatment increases the risk fivefold during use (Lutsey and Zakai, 2023). DVT is a significant medical condition that frequently occurs in traumatic orthopedics, mainly associated with periprosthetic and lower limb fractures. These fractures account for over 95% of DVT cases in traumatic orthopedics, while DVT in upper limb fractures is rare, with a global incidence of only 0.69%. DVT can lead to prolonged hospitalization and increased hospital expenses, as well as severe complications such as post-thrombotic syndrome (PTS) and PE, which can severely affect the patient's quality of life and even result in death (Hu et al., 2023).

Perioperative DVT can be classified as preoperative and postoperative, depending on the time of occurrence. Preoperative DVT is particularly concerning as it can delay surgery, affecting optimal timing and surgical outcomes. If a thrombus is not detected in time preoperatively, orthopedic surgery can cause thrombus rupture, leading to PTS, PE, and other adverse outcomes. Despite these distinctions, existing guidelines do not differentiate preoperative from postoperative DVT in terms of screening and diagnostic strategies (Hu et al, 2023).

Studies on the prevalence of preoperative DVT in patients with long bone fractures of the lower extremities suggest considerable variability. In patients with proximal femur fractures, the reported prevalence was 52.50%, while studies in Hong Kong showed a prevalence of only 5.3% without thromboprophylaxis in elderly Chinese patients with

hip fractures. One study revealed a preoperative prevalence of 43.92% in tibial plateau fractures, while another reported only 16.3% (Hu et al., 2023). These discrepancies indicate the need for standardization in screening and diagnostic practices.

Adham et al. (2021) investigated the prevalence of occult cancer in patients with unprovoked VTE. The rate of diagnosed occult cancer using the CT-based strategy was 12.8%. Yamashita (2021) revealed a prevalence of approximately 5% of upper extremity DVT among patients with DVT. In a prospective cohort, 33% of patients with upper extremity DVT had a central venous catheter or pacemaker, and 29% had active cancer. During anticoagulant therapy with DOACs, the annual incidence rates of recurrent VTE and major bleeding were 0.9% and 1.7%, respectively. After discontinuation of anticoagulant therapy with DOACs, the annual incidence rate of recurrent VTE was 3%.

DIAGNOSIS

Early diagnosis of DVT is crucial as incorrect diagnoses can lead to significant consequences. Patients incorrectly identified as having DVT (false positives) are treated with anticoagulation, exposing them to unnecessary costs, inconveniences, and bleeding risks. Conversely, patients incorrectly diagnosed as not having DVT (false negatives) risk extension and embolization of DVT in the absence of treatment (Bhatt et al., 2020).

DVT is often unilateral and should be clinically considered in patients presenting with acute pain, swelling, tenderness, edema, erythema, and/or warmth in the affected lower extremity, with the popliteal vein being a common site for DVT (Bhatt et al., 2020; Nakayama et al., 2023). Approximately 80% of PE cases result from DVT in the lower extremities (Hamamoto et al., 2022). These manifestations, however, are nonspecific, and besides preclinical risk assessment, objective tests are necessary. Early diagnosis and clinical intervention are essential for managing DVT, minimizing adverse consequences, and avoiding additional costs and risks of anticoagulant therapy for patients without the disease (Bhatt et al., 2020).

Rapid identification and efficient treatment are crucial for reducing health risks and improving clinical outcomes. Currently, various clinical, laboratory, and imaging tools are available for diagnosis. Traditional DVT diagnosis often involves CUS of the proximal leg vein. However, about 20% of DVT cases show negative results with this method, leading to the development of strategies for better screening of suspected patients. When a CUS is necessary but results negative and the D-dimer is positive, the CUS should be repeated 6 to 8 days later to assess for a possible undetected distal DVT.

The Second Consensus on Diagnosis and Treatment of DVT issued by the European Society of Cardiology (2022) and the 9th American College of Chest Physicians (2022) recommend clinical risk stratification of DVT using the Wells Score. Pre-test probability assessments, such as the Wells score, and the D-dimer test have been adopted to optimize

the diagnostic pathway, although the process can be complex and time-consuming (Appel et al., 2020). This score evaluates signs, symptoms, and VTE risk factors to categorize the probability of lower extremity DVT as low, intermediate, or high. In patients with low or intermediate risk of DVT, D-dimer level measurement is recommended. If the D-dimer is positive, whole-leg ultrasonography (US) is suggested. However, in patients with a high risk of DVT, it is recommended to perform US without measuring D-dimer levels (Hamamoto et al, 2022).

Objective diagnostic tests with high sensitivity and specificity are essential to exclude or confirm the diagnosis of DVT. Diagnostic modalities include D-dimer assays and CUS. D-dimer, a fibrin degradation product, is usually elevated in the presence of DVT. Although highly sensitive, D-dimer is often elevated in the presence of inflammation, malignancy, and other systemic diseases, being nonspecific and requiring additional tests if elevated (positive) or if the clinical probability of DVT is not low. CUS evaluates the compressibility, or lack thereof, of a venous segment to diagnose thrombosis, often associated with color Doppler to assess blood flow. In acute DVT, compressibility is lost due to passive vein distension by a thrombus. CUS can be limited to the proximal leg veins or performed on the entire leg (whole-leg CUS). US can also be performed sequentially, known as serial US (Bhatt et al., 2020).

Highly sensitive ELISA or immunoturbidimetric D-dimer tests should be measured in patients with “unlikely” clinical probability to exclude DVT diagnosis. Venous ultrasonography is recommended as the first-line imaging method for DVT diagnosis and can also be proposed in the case of confirmed PE for initial venous imaging, useful in case of suspected recurrent DVT or additional stratification in selected patients. Venous magnetic resonance imaging should be reserved for selected patients, such as in the scenario of recurrent ipsilateral DVT, a challenging diagnosis since persistent intravascular abnormalities after previous DVT often hinder compression ultrasonography diagnosis. Similarly, these residual vascular abnormalities complicate the interpretation of all other diagnostic modalities, including contrast venography.

Magnetic resonance direct thrombus imaging (MRDTI) is a technique with a short acquisition time (10 minutes) that relies on methemoglobin formation in a fresh thrombus, appearing as a high signal when viewed in a T1-weighted MRI by measuring the T1 shortening signal. This technique does not require intravenous gadolinium contrast. MRDTI can accurately diagnose a first DVT and distinguish acute recurrent DVT from chronic residual thrombotic abnormalities with sensitivity and specificity of at least 95%. MRDTI, therefore, has the potential to be used as a single test to diagnose or rule out recurrence (van Dam et al., 2020).

RECENT ADVANCES IN DVT DIAGNOSIS

Recently, the Regional Hospital of Silkeborg in Denmark implemented a new protocol for direct access to whole-leg compression ultrasonography for patients with suspected DVT referred by family doctors. It was found that a single whole-leg CUS captures distal DVT, eliminating the need for repeated CUS. This method allowed for same-day investigations, eliminating the need for additional tests such as D-dimer and significantly reducing the time and resources required for early diagnosis. The differentiated approach resulted in a remarkable decrease in resource usage compared to traditional diagnostic methods, highlighting its feasibility and effectiveness in clinical practice. The pathway did not include patients with pulmonary symptoms, which raise the suspicion of pulmonary embolism. In Denmark, these patients are referred directly to critical care procedures. Sixty percent of all patients were seen with an average time of 24 minutes without the need for hospitalization. The direct same-day pathway provided approximately 60% reduction in resource usage (Appel et al., 2020).

Whole-leg CUS and proximal leg CUS are clinically equivalent methods for diagnosing DVT. Whole-leg CUS has the advantage of not requiring repetitions to detect if an isolated distal venous thrombosis has progressed to proximal veins, reducing hospital visits. However, its frequent use may increase the detection of distal thromboses, raising concerns about overtreatment, given that isolated distal deep vein thrombosis (IDDVT) is generally considered less severe. Studies highlight the importance of surveillance to prevent late complications such as post-thrombotic syndrome. Additionally, whole-leg CUS can identify other pathologies, improving overall diagnostic efficiency. Thus, while effective, its use should be balanced with considerations of potential clinical impacts and costs associated with the treatment of detected IDDVT (Appel et al., 2020).

An Italian study used the Nominal Group Technique (NGT) to reach consensus among experts on the management of DVT and pulmonary embolism in the emergency department. Despite advances, many low-risk patients are unnecessarily admitted, suggesting the need for clear guidelines for outpatient management. Experts reviewed recent evidence and developed consensus statements that address from initial suspicion to acute treatment of these conditions. Recommendations such as the use of the Wells score for risk stratification, D-dimer testing, and the preference for DOACs were highlighted as fundamental for evidence-based clinical practice. The application of NGT proved effective in integrating clinical and scientific perspectives, promoting standardization and continuous improvement in the quality of emergency healthcare. This structured approach not only facilitates early and accurate diagnosis but also optimizes patient management, resulting in better clinical outcomes and efficiency in care (Salvi et al., 2020).

Due to high morbidity and mortality in hospitalized patients and diagnostic criteria failures, a study was conducted at Kagoshima University between January 2017 and

December 2018 on patients undergoing planned surgery under general anesthesia. The aim was to develop a new pre-test probability score for DVT diagnosis in patients before surgery under general anesthesia, considering: D-dimer greater than or equal to 1.5 (2 points), age over 60 years (1 point), positive family history of DVT (1 point), glucocorticoid use (1 point), high-risk cancer for DVT (1 point), and prolonged immobilization (1 point). The Kagoshima-DVT score divided patients into low, medium, and high-risk groups, considering scores from 0 to 7. The initial probability score proved effective in diagnosing DVT in hospitalized and outpatient patients before surgery. It was possible to distinguish a low-probability group that did not require full-leg ultrasonography and a high-probability group that had more DVT cases identified before surgery (Hamamoto et al., 2022).

Another recent study, named Theia, was a diagnostic management study conducted in 5 university hospitals and 7 non-academic hospitals in 5 countries. Between March 2015 and March 2019, patients aged 18 years or older presenting with clinical suspicion of acute recurrent ipsilateral leg DVT were included. The aim of the research was to evaluate the use of direct thrombus magnetic resonance imaging (ITMR), a technique without the need for intravenous contrast and with a 10-minute acquisition time, capable of accurately differentiating acute recurrent DVT from chronic residual thrombi. The safety of ITMR as the only test to rule out recurrent ipsilateral DVT was evaluated. Patient treatment was determined based on the ITMR result, performed within 24 hours after inclusion in the study. The study concluded that the rate of new VTE episodes after a negative ITMR result was low. This exam proved to be a simple, practical, and reliable diagnostic tool (van Dam et al., 2020).

TREATMENT

Acute DVT can be treated on an outpatient basis with anticoagulant therapy, reserving hospitalization for patients with severe symptoms. Initially, hospital treatment involves intravenous heparin use, followed by a transition to oral or subcutaneous anticoagulant therapy for three months. In more complex cases, invasive treatment options are indicated, such as catheter-directed thrombolysis (CDT), pharmacomechanical CDT, and percutaneous mechanical thrombectomy (PMT) (Sailer et al., 2022).

CDT and pharmacomechanical CDT require ICU admission, representing a significant economic burden on the healthcare system. In contrast, PMT does not use thrombolytic agents, reducing bleeding risk and eliminating the need for ICU admission. This technique allows the removal of all types of thrombi, including subacute and chronic clots. Indications for invasive treatments include emergencies such as threatened limb or clot progression in the inferior vena cava during anticoagulant therapy, anticoagulant therapy failure, prevention of post-thrombotic syndrome (PTS), or progression of PTS in patients with iliofemoral DVT or moderate to severe PTS (Sailer et al., 2022).

Phlegmasia cerulea dolens is a rare but potentially fatal complication of acute DVT, characterized by severe limb swelling, pain, and cyanosis, potentially leading to arterial ischemia and gangrene, with high amputation and mortality rates. Iliofemoral DVT differs from femoropopliteal DVT as it is associated with more frequent recurrences and more severe PTS due to the anatomical characteristics of the lower limb venous system. While femoropopliteal or distal DVT is more easily compensated by collateralization, iliofemoral occlusion has little chance of sufficient collateralization. However, some cases develop adequate collateralization, directing venous return to the ipsilateral and contralateral iliac system, quickly relieving symptoms (Kim; Choi and Kim, 2021).

For asymptomatic proximal DVT, anticoagulant treatment alone is sufficient to reduce recurrence rates and prevent PE. There is no need for endovascular thrombus removal in patients with isolated distal DVT, as the risk of PE is low. The need for anticoagulant treatment for isolated distal DVT has not yet been established, varying between centers and clinicians (Kim; Choi and Kim, 2021).

Minimally invasive techniques have been used in DVT treatment, such as autonomous percutaneous mechanical thrombectomy, which fragments and aspirates thrombi; catheter-directed pharmacomechanical thrombolysis (PCDT), combining CDT with PMT; stent placement, especially in cases of iliac vein or inferior vena cava (IVC) obstruction; and concomitant anticoagulant treatment with unfractionated heparin during and after endovascular procedures. These techniques have been effective in reducing acute symptoms and preventing complications such as post-thrombotic syndrome (Kim; Choi and Kim, 2021).

Direct oral anticoagulant therapy has also been a safe and efficient approach to preventing recurrences, although its effectiveness as monotherapy in severe DVT cases is limited. Studies indicate that these combined approaches not only accelerate recovery but also reduce treatment time and the need for hospitalization, providing a better quality of life for patients (Kim; Choi and Kim, 2021).

REFERENCES

ADHAM, Salma, et al. Bilateral deep vein thrombosis: Time to screen for occult cancer?. **Vascular Medicine**, v. 26, n. 6, p. 660-661, 2021.

APPEL, Charlotte W. et al. Direct-access to sonographic diagnosis of deep vein thrombosis in general practice: a descriptive cohort study. **BMC Family Practice**, v. 21, n. 1, p. 195, 2020.

BHATT, Meha, et al. Diagnosis of deep vein thrombosis of the lower extremity: a systematic review and meta-analysis of test accuracy. **Blood advances**, v. 4, n. 7, p. 1250-1264, 2020.

BORGEL, Delphine, et al. Inflammation in deep vein thrombosis: a therapeutic target?. **Hematology**, v. 24, n. 1, p. 742-750, 2019.

BRILL, Alexander. Multiple facets of venous thrombosis. **International Journal of Molecular Sciences**, v. 22, n. 8, p. 3853, 2021.

GALANAUD, J.-P., et al. Isolated distal deep vein thrombosis: What have we learnt from the OPTIMEV study?. **JMV-Journal de Médecine Vasculaire**, v. 48, n. 1, p. 3-10, 2023.

HAMAMOTO, Yuki, et al. A new pre-test probability score for diagnosis of deep vein thrombosis in patients before surgery. **Journal of Cardiology**, v. 79, n. 5, p. 664-670, 2022.

HU, Yaowen, et al. Prevalence of preoperative deep vein thrombosis in long bone fractures of lower limbs: a systematic review and meta-analysis. **Journal of Orthopaedics and Traumatology**, v. 24, n. 1, p. 19, 2023.

JIANG, Weiguang, et al. Metabolomic profiling of deep vein thrombosis. **Phlebology**, v. 39, n. 3, p. 154-168, 2024.

KHAN, Faizan, et al. Venous thromboembolism. **The lancet**, v. 398, n. 10294, p. 64-77, 2021.

KHAN, Oneib; MARMARO, Ashley; COHEN, David A. A review of upper extremity deep vein thrombosis. **Postgraduate Medicine**, v. 133, n. sup1, p. 3-10, 2021.

KIM, Kyung Ah; CHOI, Sun Young; KIM, Ran. Endovascular treatment for lower extremity deep vein thrombosis: an overview. **Korean Journal of Radiology,** v. 22, n. 6, p. 931, 2021.

LI, Da, et al. Synergic effect of GPIBA and von Willebrand factor in pathogenesis of deep vein thrombosis. **Vascular**, v. 28, n. 3, p. 309-313, 2020.

LUTSEY, Pamela L.; ZAKAI, Neil A. Epidemiology and prevention of venous thromboembolism. **Nature Reviews Cardiology**, v. 20, n. 4, p. 248-262, 2023.

NAKAYAMA, Yusuke, et al. Deep learning-based classification of adequate sonographic images for self-diagnosing deep vein thrombosis. **Plos one**, v. 18, n. 3, p. e0282747, 2023.

SAILER, Anne, et al. Deep vein thrombosis: Update on mechanical thrombectomy and intravascular US. **RadioGraphics**, v. 42, n. 6, p. E184-E185, 2022.

SALVI, Aldo, et al. Diagnosis and Treatment of Deep Vein Thrombosis in the Emergency Department: Results of an Italian Nominal Group Technique Study. **Clinical and Applied Thrombosis/Hemostasis,** v. 26, 2020.

VAN DAM, Lisette F., et al. Magnetic resonance imaging for diagnosis of recurrent ipsilateral deep vein thrombosis. **Blood, The Journal of the American Society of Hematology**, v. 135, n. 16, p. 1377-1385, 2020.

YAMASHITA, Yugo. Deep vein thrombosis of upper extremities in the era of direct Oral anticoagulants. **International Journal of Cardiology**, v. 339, p. 164-165, 2021.

YAO, Mengting, et al. Neutrophil extracellular traps mediate deep vein thrombosis: From mechanism to therapy. **Frontiers in Immunology,** v. 14, p. 1198952, 2023.

Chapter 21

THORACIC TRAUMA

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CHAPTER 21

THORACIC TRAUMA

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Thoracic trauma represents one of the most frequent and harmful injuries in polytrauma. Besides the direct effects of mechanical injury caused by the impact itself, pulmonary integrity and function are also compromised by the systemic release of inflammatory mediators due to additional injuries in other body regions (Horst and Hildebrand, 2020). More than two-thirds of

blunt thoracic traumas in developed countries are caused by motor vehicle collisions, while the remainder results from falls from height or direct impact to the chest. Penetrating chest injuries include gunshot wounds, stabbings, explosions, and penetration by other objects (including workplace and sports injuries, such as archery). Ballistic injuries are one of the main causes of morbidity and mortality in the United States and often involve the chest (Lewis *et al.*, 2021).

Recent studies, such as those by Huang *et al.* (2019), have evaluated the relevance of post-trauma complications and observed that, over eight years, chest injuries were a significant risk factor for the development of acute respiratory distress syndrome (ARDS). The mechanism of injury is crucial to predict the need for intervention, as penetrating injuries are more likely to require surgical exploration (Stretch). The Advanced Trauma Life Support (ATLS) Guidelines (ACS, 2018) recommend emergency surgical intervention for patients with blunt and penetrating trauma if initial hemorrhagic loss is less than 1,500 mL of fluid, but with ongoing bleeding that may require thoracotomy, based on the continuous blood loss rate (200 mL/h for 2 to 4 hours), considering the patient's physiological state.

According to Lewis *et al.* (2021), thoracic trauma occurs in about 60% of polytrauma patients and presents a wide range of mortality, globally estimated at 10%. In more severe cases, such as closed polytrauma with bilateral pulmonary contusions and hemopneumothorax, mortality can exceed 50%. Severe rib fractures lead to immobilization, inadequate breathing, and suppression of coughing, contributing to approximately a 30% increase in the risk of developing pneumonia in these patients (Beloy *et al.*, 2022).

Imaging plays a fundamental role in the diagnosis and treatment of pulmonary trauma; however, chest X-rays may not diagnose most fractures, with computed tomography (CT) being more sensitive to help assess injury severity and identify additional findings that may alter the therapeutic approach. CT, however, can fail to diagnose, especially in non-displaced, chondral, or anterior fractures (Caragounis; Xiao and Granhed, 2019). It is crucial to identify and appropriately treat patients at higher risk of complications. The use of analgesics may be indicated to avoid respiratory complications, pneumonia, and atelectasis, while in some patients, surgical fixation is more appropriate (Simon; Wickham, 2019).

Trends in techniques and diagnostic methods have evolved significantly, as discussed by Marro *et al.* (2019) and Horst; Hildebrand (2020). These studies highlight the growing adoption of advanced technologies, such as artificial intelligence and machine learning, to enhance the accuracy and efficiency of medical diagnoses. Additionally, there is a renewed focus on personalized medicine, using genomic data and biomarkers to develop targeted therapies. These approaches promise not only to revolutionize clinical practice but also to transform traditional healthcare standards, making them more tailored to individual patient needs.

EPIDEMIOLOGY

Understanding the epidemiology of thoracic trauma is crucial for guiding prevention strategies and improving patient care. According to Lundin *et al.* (2022), the prevalence of chest injuries among trauma patients was 32%. These patients exhibited distinct injury patterns according to age. Older individuals (≥60 years) tend to have a higher proportion of rib fractures, while younger individuals (<60 years) suffer more from internal thoracic organ injuries, such as pneumothorax, pulmonary contusion, and vascular injury.

In terms of demographic data, the typical chest injury patient was a middle-aged man (Elgar; Smiley and Latifi, 2022). Blunt trauma, such as falls and car accidents, was the predominant injury mechanism. This population showed greater injury severity, with higher median scores on severity scales (ISS and NISS), compared to trauma patients without chest injuries. The differences in injury patterns across age groups indicate the need for specific therapeutic approaches for each group (Lundin *et al.*, 2022).

Thoracic trauma is responsible for a significant portion of trauma admissions, ranging between 10% and 15%, and for 25% to 35% of trauma deaths, given that the chest houses vital organs such as the heart, lungs, major vessels, and esophagus (Orlas *et al.*, 2020; Lundin et al., 2022; Birse et al., 2020). Besides contributing substantially to morbidity, thoracic trauma imposes a significant financial burden on the healthcare system (Elgar; Smiley and Latifi, 2022).

A study conducted by Caragounis, Xiao, and Granhed revealed that traffic accidents are the main cause of chest trauma among young people (62%), especially motorcycle accidents (29%), while falls predominate among older patients (59%). According to Elgar, Smiley, and Latifi, high-speed traffic accidents result in blunt thoracic trauma in approximately 60% of polytraumatized patients, with a mortality rate of 20% to 25%. The higher the frequency of invasive diagnostic and therapeutic procedures, the higher the mortality rates.

Previous studies indicate that elderly patients have worse outcomes after blunt thoracic trauma, possibly due to the presence of comorbidities. Additionally, the higher prevalence in men may be related to more common activity patterns and risk behaviors in this group. Regarding environmental factors, the severity of thoracic trauma, such as the number of rib fractures and the presence of pulmonary contusion, plays a crucial role in prognosis. As for lifestyle factors, the presence of comorbidities such as respiratory diseases, liver diseases, and coagulopathies significantly increases the risk of mortality in this population (Elgar; Smiley and Latifi, 2022).

Thoracic trauma represents a significant cause of global mortality and morbidity, especially among young adults. In Cali, Colombia, these injuries rank third in causes of death due to homicides, behind TBI and polytrauma, and fourth in traffic accidents (Orlas et al., 2020).

Complications such as pneumonia or respiratory failure occur in 16.2% of patients over 65 years old and in 28.6% of patients over 85 years old who suffered isolated closed

thoracic trauma. In the elderly, minor pulmonary contusions are associated with double the risk of mortality and longer hospital stays, despite having few consequences in healthy young people (Simon and Wickham, 2019).

Severe rib fractures, such as hemothorax or pneumothorax, are more common in people over 65 years old, significantly increasing mortality compared to younger individuals. Data from the US National Trauma Data Bank show that the number of fractured ribs correlates with an increased risk of pneumonia and/or death, especially with multiple fractures (Simon and Wickham, 2019).

Studies indicate that 35% of trauma-related deaths in the US are due to blunt thoracic trauma, with one in four trauma patients dying from chest injuries (Dogrul et al., 2022). High-speed accidents result in blunt thoracic trauma in about 60% of polytrauma patients, with a mortality rate between 20% and 25% (Elgar; Smiley and Latifi, 2022).

Rib fractures are common in approximately 40% of patients with closed thoracic trauma, contributing to higher morbidity, injury severity, and mortality. Elderly patients with rib fractures generally have less severe injuries and lower Injury Severity Scores (ISS) compared to younger patients, although they have higher mortality rates (Caragounis; Xiao and Granhed, 2021).

Advanced age is a significant factor for rib fractures, with a higher proportion among occupants aged 65 years or older compared to younger individuals. With aging, the chest's ability to absorb impacts decreases due to bone demineralization and rib deterioration, increasing their susceptibility to fractures (O'Donovan *et al.*, 2022).

DIAGNOSIS

Thoracic injuries are common in trauma cases and can be categorized as blunt or penetrating. After initial evaluation, these injuries are classified according to the associated life risk: immediate, fatal, or potentially fatal (Okoye *et al.*, 2023). In severe chest traumas, early mortality is significant, highlighting the need for rapid physical assessments and imaging tests for accurate injury identification (Wong *et al.*, 2023). Early detection is crucial to guide treatment and appropriate patient referral, avoiding acute complications (Chan *et al.*, 2020).

A systematic approach in the initial evaluation facilitates the identification of injuries requiring immediate intervention. Physical examination and chest X-ray are generally sufficient to diagnose many injuries, while bedside ultrasound, such as extended FAST, is effective in detecting life-threatening injuries (Chan et al., 2020). Although radiography is the main diagnostic resource, computed tomography (CT) is more sensitive in specific cases and should be used cautiously in unstable patients (Okoye *et al.*, 2023).

The "ABC-Please" approach is used to interpret thoracic findings in trauma, with "A" (abnormal air) referring to the predominance of pneumothorax and pneumomediastinum,

often benign and associated with interstitial pulmonary lacerations. These cases generally present symptoms such as dyspnea and chest pain, potentially leading to severe complications if not properly treated (Chan *et al.*, 2020; Wong *et al.*, 2023). “B” (abnormal bones) indicates that thoracic spine fractures are often associated with rib fractures, with an incidence ranging from 10% to 70% in patients undergoing CT scans. “C” (abnormal cardiovascular system) highlights the importance of contrast-enhanced chest CT in detecting direct and indirect aortic injuries, such as contrast extravasation and periaortic hematoma, as well as identifying massive hemothorax (Wong *et al.*, 2023). Finally, “Please” (abnormal parenchyma and pulmonary vessels) covers lung parenchymal injuries, such as contusions and lacerations, which are common in 75% of blunt thoracic trauma cases. These injuries can progress to complications, including pneumonia, lung abscess, bronchopleural fistula, and acute respiratory distress syndrome (ARDS). Rupture of pulmonary arterial pseudoaneurysms can result in massive hemoptysis and impairment of alveolar gas exchange (Wong*et al.*, 2023).

Volumetric chest CT is ideal for diagnosis in stable patients and can be performed with contrast for detailed evaluation, ensuring safety and good communication between teams (Wong *et al.*, 2023). However, there are debates about its use due to potential iatrogenic side effects, especially in cases of stab wounds with normal chest X-ray outside the thoracoabdominal zone (Augustin *et al.*, 2020). The initial clinical examination, according to Reichardt *et al.*(2020), should not be replaced by diagnostic tests, being crucial for the prognosis of trauma victims.

Trauma patients are primarily clinically evaluated to identify life-threatening conditions, requiring resuscitation with intravenous fluids, blood products, intubation, or thoracostomy, according to ATLS protocols (Chan *et al.*, 2020). Chest X-ray is recommended as an initial diagnostic complement, essential to identify critical thoracic conditions such as hemothorax, pneumomediastinum, pulmonary contusion, or rib fractures (Chan *et al.*, 2020; Wong et al., 2023).

According to Wong (2022), rapid physical and radiographic assessments play crucial roles in identifying severe thoracic traumas. Chest X-ray is frequently used in trauma patients to identify life-threatening conditions. Current ATLS guidelines recommend chest X-ray as a complement to the primary assessment in initial trauma care (ATLS, 2012). This diagnostic tool is commonly employed to identify thoracic injuries such as hemothorax, pneumomediastinum, pulmonary contusion, or rib fracture. During acute resuscitation, the trauma patient is generally kept supine until a complete assessment is performed. Performing a chest X-ray in this position requires time, resources, and equipment, potentially delaying the diagnosis and treatment of pneumothorax (Chan *et al.*, 2020).

While chest X-rays, even when repeated, may not detect some injuries, such as small pneumothorax, chest CT avoids repeated X-rays and offers greater sensitivity, especially for anterior and small pneumothorax. However, despite greater sensitivity, CT may only reveal

minor new findings without significantly impacting the management of penetrating thoracic trauma (Augustin *et al.*, 2019). Additionally, CT exposes the patient to an estimated ionizing radiation dose of 7 mSv, equivalent to two years of natural background radiation exposure, and may cause allergic reactions to contrast. Depending on the patient's condition, emergency thoracotomy may be performed at any time during trauma resuscitation (Chan *et al.*, 2020).

TREATMENT

Due to its severity, identifying thoracic injuries should be a priority in caring for polytrauma patients (Marro *et al.*, 2019). It is essential to predict an adequate prognosis and conduct an effective assessment of thoracic trauma severity for proper management (Mukerji et al., 2021). Effective treatment requires a multidisciplinary approach, including analgesia, stabilization of flail chest, hemodynamic resuscitation, and ventilatory support. Additionally, chest drains may be necessary for managing hemothorax and pneumothorax (Cheruvu *et al.*, 2023).

Cases of flail chest, defined as a fracture of three or more sequential ribs resulting in paradoxical chest wall movement, can be treated conservatively or surgically. Conservative treatment involves adequate pain control using oxygenation, opioid analgesia, intercostal nerve block, neuraxial block, and epidural catheter. Surgical treatment includes stabilization with plates and intramedullary stabilization. Immobilizing the flail chest segments aims to minimize movement during breathing to avoid ineffective ventilation and secondary respiratory failure (Cheruvu *et al.*, 2023; Marro *et al.*, 2019; Hisamune *et al.*, 2024).

In cases of acute respiratory distress syndrome (ARDS) caused by thoracic trauma, management includes mechanical ventilation with lung protective techniques and alveolar recruitment maneuvers (Dagod *et al.*, 2021). However, prolonged mechanical ventilation is associated with high rates of pneumonia, tracheostomy, and barotrauma, among other complications (Hisamune *et al.* 2024).

When thoracic trauma is penetrating, treatment and consequences are directly related to the severity of damage to internal organs, especially respiratory failure caused by airway obstruction and bleeding. The primary goal in ensuring an adequate airway is to improve ventilation and prevent air leaks into adjacent areas using an endotracheal tube with a balloon positioned below the injury site. Penetrating airway injuries can quickly progress to airway obstruction and respiratory failure. When endotracheal intubation is not feasible, emergency tracheostomy becomes the only appropriate option. In cases of tracheal injuries, it is preferable to position the tracheostomy in the affected area to preserve the normal portion of the trachea, facilitating subsequent surgical repair (Cakmak *et al.*, 2022).

Traumas resulting in pneumothorax and hemothorax can be treated with chest drains. In cases of hemothorax with significant hemorrhage and active bleeding due to

costal artery injury, exploratory thoracotomy, assisted video thoracoscopy, or embolization by interventional radiology may be necessary (Marro *et al.*, 2019). Massive hemothorax can result in the absence of breath sounds on the affected side. Blood pressure should be stabilized with rapid fluid administration, and a chest drain should be inserted. Patients with worsening subcutaneous emphysema, progressive pneumomediastinum, pneumothorax with continuous leakage, persistent pneumothorax despite the chest drain, or esophageal wall prolapse towards the trachea should undergo emergency surgery (Cakmak *et al.*, 2022).

The approach to treating rib fractures can be classified into two main categories: conservative treatment and surgical treatment. Although conservative treatment was the main choice in the past, surgical stabilization of rib fractures (SSRF) has increased substantially in the past ten years (Hisamune *et al.*, 2024). Isolated rib fractures are treated conservatively with effective pain control, essential to avoid blood gas disturbances, atelectasis, and pneumonia caused by hypoventilation due to pain. However, rib fractures can be accompanied by pulmonary contusions, pneumothorax, and hemothorax, which can arise late. Therefore, in patients with known rib fractures who present worsening, it is highly recommended to perform new imaging to assess the progression of the thoracic injury (Marro *et al.*, 2019). Surgical treatment, based on SSRF (Surgical Stabilization of Rib Fractures), uses fundamental orthopedic principles of realignment and fixation to treat rib fractures, restoring chest wall stability, reducing pain, and improving compromised respiratory function (Hisamune *et al.*, 2024).

DOUBLE-LUMEN MECHANICAL VENTILATION

Various clinical manifestations can occur after thoracic trauma, with airway maintenance being the primary initial conduct. In a case of severe thoracic trauma, a patient underwent thoracotomy and mechanical ventilation with a double-lumen tube. Despite the endotracheal tube, oxygen saturation remained low due to severe left lung contusion. A rupture of the tracheal membrane up to the carina, with a 0.5x0.5 cm cavity in the carina membrane, was identified. Due to the patient's lateral position, the use of ECMO (extracorporeal membrane oxygenation) was not possible. To improve breathing, an innovative method called "double-lumen mechanical ventilation" was proposed and applied. This method involved inserting a single-lumen tube into the right intermediate bronchus for ventilation of the right middle and lower lobes. This procedure significantly improved the patient's oxygen saturation, which remained around 98%. During the operation, a myocutaneous flap was used to cover the carina defect, and the tracheal membrane was repaired. The patient was discharged without complications after seven days (Shen and Ma, 2020).

VENO-VENOUS ECMO (VV-ECMO) THERAPY AND INDEPENDENT LUNG VENTILATION (ILV)

Studies demonstrate one of the first cases of massive air leakage after heterogeneous thoracic trauma associated with refractory hypoxemia, successfully treated with a combination of veno-venous ECMO (vv-ECMO) and independent lung ventilation (ILV). Vv-ECMO has proven to be a reliable rescue strategy for acute respiratory distress syndrome (ARDS) in traumatized patients, even with bleeding risk, improving outcomes and reducing the need for extensive surgeries. In cases where one side of the lung presents significant collapse, causing severe hypoxemia, ILV allows adequate ventilation for each lung, aiding in the healing of the leaking lung and keeping the healthy lung open. Although ILV is challenging, it can reduce complications and the time to wean from ECMO. In summary, vv-ECMO is a valuable rescue strategy for traumatic airway leaks, allowing consideration of non-operative management or minimized pulmonary resection (Cheruvu*et al.*, 2023).

CHALLENGES IN TREATING THORACIC TRAUMA

Treating thoracic trauma faces unique challenges that go beyond conventional and innovative approaches, requiring deep understanding and specific strategies to overcome them and promote adequate patient care. One of the biggest challenges is the complexity and variety of injuries that can occur, such as pneumothorax, hemothorax, pulmonary contusions, rib fractures, and major vessel injuries (Cheruvu *et al.*, 2023). Maintaining a patent airway and controlling bleeding are critical and challenging, often requiring invasive procedures that must be performed carefully not to aggravate injuries (Cakmak *et al.*, 2022). Controlling bleeding, especially from major vessels, requires a quick and effective response to avoid hemorrhagic shock and ensure patient survival (Schmitt *et al.*, 2021).

Intense pain is a constant in thoracic trauma, and its proper management becomes a challenge. It not only affects the patient's quality of life but can also compromise breathing and mobility, increasing the risk of complications (Mukerji *et al.*, 2021; Schmitt *et al.*, 2021). Pulmonary complications, such as pneumonia and acute respiratory distress syndrome (ARDS), also represent significant challenges in managing thoracic trauma, as they can develop rapidly and require constant vigilance and intensive care (Dagod *et al.*, 2021).

The rapid evolution of medical technologies presents both opportunities and challenges. Adapting to new diagnostic and treatment technologies, such as advanced imaging techniques and minimally invasive procedures, requires continuous training and updating of professionals involved in patient care with thoracic trauma. The need for a multidisciplinary approach is another important aspect, requiring the collaboration of a diverse team of highly skilled professionals (Cheruvu *et al.*, 2023).

To overcome the challenges in treating thoracic trauma, specific strategies are necessary. Investing in the continuous training and updating of professionals is fundamental

to deal with the complexities of thoracic trauma and new treatment technologies (Cheruvu *et al.*, 2023). Developing and implementing care protocols is essential to ensure a cohesive and efficient approach to treating these patients (Cheruvu *et al.*, 2023). Research and innovation also play a crucial role, as developing new diagnostic and treatment techniques is fundamental to improving patient outcomes (Dagod *et al.*, 2021). Finally, adopting a patient-centered approach, considering their specific treatment and recovery needs, is indispensable for providing quality and personalized care (Schmitt *et al.*, 2021).

Moreover, the team must be trained to quickly identify and control internal bleeding, particularly from major vessels or thoracic organs. This often requires a combination of advanced diagnostic techniques and immediate surgical interventions. CT plays a crucial role in this context, allowing for a more accurate assessment of rib fractures and pulmonary complications, although it requires the patient's clinical stability to be performed (Mukerji *et al.*, 2021).

Recovery for patients with thoracic trauma often involves long-term challenges, including pulmonary rehabilitation and managing sequelae such as pulmonary dysfunction and chronic pain. Pulmonary rehabilitation, an integral part of recovery, aims to improve lung function, exercise capacity, and quality of life (Cheruvu *et al.*, 2023).

REFERENCES

AUGUSTIN, Pascal, *et al.* Usefulness of CT-scan in the management of chest stab trauma: a prospective observational study. **European Journal of Trauma and Emergency Surgery,** v. 46, p. 1385-1391, 2020.

BELOY, Victoria; DULL, Matthew. Blunt chest wall trauma: Rib fractures and associated injuries. **JAAPA**, v. 35, n. 11, p. 25-31, 2022.

BIRSE, Fraser, *et al.* Blunt chest trauma in the elderly: an expert practice review. **Emergency Medicine Journal**, v. 37, n. 2, p. 73-78, 2020.

CAKMAK, Gul, *et al.* Airway management in penetrating thoracic trauma. **Anaesthesiology Intensive Therapy**, v. 54, n. 3, p. 253-261, 2022.

CARAGOUNIS, Eva-Corina; XIAO, Yao; GRANHED, Hans. Mechanism of injury, injury patterns and associated injuries in patients operated for chest wall trauma. **European journal of trauma and emergency surgery**, v. 47, p. 929-938, 2021.

CHAN, Kenneth K., *et al.* Chest ultrasonography versus supine chest radiography for diagnosis of pneumothorax in trauma patients in the emergency department. **Cochrane database of systematic reviews**, n. 7, 2020.

CHERUVU, M. S., *et al.* Chest wall reconstruction reduces hospital mortality following major chest wall trauma: a retrospective cohort study. **The Annals of The Royal College of Surgeons of England**, v. 105, n. 6, p. 489-500, 2023.

DAGOD, Geoffrey, *et al*. A combined management with vv-ECMO and independent lung ventilation for asymmetric chest trauma. **General Thoracic and Cardiovascular Surgery**, v. 69, p. 902-905, 2021.

ELGAR, Guy; SMILEY, Abbas; LATIFI, Rifat. Major risk factors for mortality in elderly and non-elderly adult patients emergently admitted for blunt chest wall trauma: hospital length of stay as an independent predictor. **International Journal of Environmental Research and Public Health**, v. 19, n. 14, p. 8729, 2022.

HISAMUNE, Ryo, *et al.* A meta-analysis and trial sequential analysis of randomised controlled trials comparing nonoperative and operative management of chest trauma with multiple rib fractures. **World Journal of Emergency Surgery,** v. 19, n. 1, p. 11, 2024.

HORST, Klemens; HILDEBRAND, Frank. Focus on chest trauma: implications from clinical and experimental studies. **European Journal of Trauma and Emergency Surgery**, v. 46, p. 1-2, 2020.

LEWIS, Brittany T., *et al*. Imaging manifestations of chest trauma. **Radiographics**, v. 41, n. 5, p. 1321-1334, 2021.

LUNDIN, Andrea, *et al*. Thoracic injuries in trauma patients: epidemiology and its influence on mortality. **Scandinavian journal of trauma, resuscitation and emergency medicine**, v. 30, n. 1, p. 69, 2022.

MARRO, Alessandro, *et al*. Blunt chest trauma: classification and management. **Emergency radiology**, v. 26, p. 557-566, 2019.

MUKERJI, Saptarshi, *et al*. Retrospective validation of a risk stratification tool developed for the management of patients with blunt chest trauma (the STUMBL score). **Emergency Medicine Australasia**, v. 33, n. 5, p. 841-847, 2021.

O'DONOVAN, Siobhan, *et al*. Fatal blunt chest trauma: an evaluation of rib fracture patterns and age. **International Journal of Legal Medicine**, v. 136, n. 5, p. 1351-1357, 2022.

OKOYE, O. G., *et al.* Analysis of Diagnoses of Chest Injuries in a Nigerian Trauma Center. **Nigerian Journal of Clinical Practice**, v. 26, n. 8, p. 1134-1138, 2023.

ORLAS, Claudia P., *et al*. Chest trauma outcomes: public versus private level I trauma centers. **World journal of surgery**, v. 44, n. 6, p. 1824-1834, 2020.

REICHARDT, Gabriel Sebben, *et al.* CT scanning in blunt chest trauma: validation of decision instruments. **Revista do Colégio Brasileiro de Cirurgiões,** v. 47, p. e20202648, 2020.

SCHMITT, J., *et al*. Damage control management of a major chest trauma by intracorporeal quick clot combat gauze application. **Respiratory Medicine and Research**, v. 79, 2021.

SHEN, Cheng; MA, Lin. New acute respiratory management in tracheal rupture caused by chest trauma. J**ournal of Cardiothoracic Surgery**, v. 15, p. 1-3, 2020.

SIMON, Jonathan B.; WICKHAM, Alex J. Blunt chest wall trauma: an overview. British **Journal of Hospital Medicine**, v. 80, n. 12, p. 711-715, 2019.

STRETCH, Benjamin; KYLE, Amy; PATEL, Mihir. Management of penetrating chest trauma in the context of major trauma networks. **British Journal of Hospital Medicine**, v. 83, n. 10, p. 1-7, 2022.

WONG, Yon-Cheong, et al. Watch Out for the Early Killers: Imaging Diagnosis of Thoracic Trauma. **Korean journal of radiology**, v. 24, n. 8, p. 752, 2023.

Chapter 22

OCULAR TRAUMA

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CHAPTER 22

OCULAR TRAUMA

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Ocular trauma is a global public health issue with significant impacts on patients’ quality of life. Structural changes in the eye due to trauma can lead to severe consequences, including permanent visual impairment. According to the World Health Organization (WHO), approximately 55 million people seek medical attention due

to ocular injuries annually, and more than 75% of those affected become blind in one eye (Pouchain *et al.*, 2020; Jayme *et al.*, 2023; Balakrishnan *et al.*, 2020). The incidence of ophthalmic emergencies is higher among young men aged 20 to 40 years due to greater exposure to hazardous work environments. Ocular trauma is also common in childhood and adolescence, being a significant concern in pediatric ophthalmic care (Guevara, 2024).

Orbital anatomy, including the orbital floor composed of the maxillary, zygomatic, and palatine bones, and the lamina papyracea, is frequently affected in orbital traumas (Lozada, Cleveland, Smith, 2019). Ocular traumas can be caused by physical, chemical, or electrical agents and are classified into open and closed traumas. Closed trauma, more common, results from contusions and collisions, while open trauma involves cuts or perforations of the eyeball, posing an immediate risk of infection (Gomes; Castro e Silva; Ribeiro, 2019). Open globe injuries are classified into anatomical zones, with initial treatment focusing on watertight wound closure to allow healing and preparation for future surgeries (Razeghinejad *et al.*, 2020).

The initial diagnosis of ocular trauma involves a comprehensive evaluation, including visual acuity tests, pupillary reaction, intraocular pressure, and visual field tests (Gomes; Castro e Silva; Ribeiro, 2019). Advanced techniques like Optical Coherence Tomography (SD-OCT) and Fundus Autofluorescence (FAF) are used to assess retinal damage and visual prognosis (Mahesh *et al.*, 2019). Computed tomography (CT) is preferred for evaluating orbital fractures and bone injuries due to its high resolution and speed. B-scan ultrasound and Ultrasonic Biomicroscopy (UBM) are effective in detecting lesions in the posterior and anterior segments, respectively (Gomes; Castro e Silva; Ribeiro, 2019). Magnetic resonance imaging (MRI) is useful for detailed visualization of orbital structures, although contraindicated in cases of magnetic foreign bodies (Mahesh *et al.*, 2019).

Preventing ocular traumas is crucial, as recurrence is three times more likely after the first incident (Guevara, 2024). Public awareness measures on the importance of using personal protective equipment (PPE) and seeking immediate medical attention are essential. Additionally, it is vital that emergency physicians are adequately trained to handle ophthalmic emergencies, improving patient prognosis and avoiding irreversible damage (Jayme *et al.*, 2023). Detailed anatomical assessment through CT is indispensable for diagnosing intracranial injuries resulting from facial fractures, and early detection of these injuries can significantly reduce patient morbidity (Balakrishnan *et al.*, 2020).

EPIDEMIOLOGY

Ocular trauma is frequently encountered in ophthalmic emergencies, with higher incidence among young men, particularly those aged 20 to 40 years (Guevara, 2024; Cheung *et al.*., 2014). The main causes include workplace accidents in construction and agriculture, as well as inadequate care during childhood and adolescence (Guevara, 2024).

The incidence tends to be higher in urban areas due to exposure to risky activities and traffic accidents (Cheung *et al.*, 2014).

In the United States, ophthalmic emergencies account for about 3% of emergency department visits. In Brazil, this percentage is significantly higher, representing 13.6% of total admissions (Jayme *et al.*, 2023). Ocular trauma is the leading cause of unilateral blindness in the United States, affecting about 40,000 of the 60,000 patients who suffer ocular injuries annually. Men have a higher incidence compared to women due to greater exposure to high-risk work environments, such as agriculture and construction. The prevalence is estimated at 42.5% in young adults aged 20 to 40 years (Gomes; Castro e Silva; Ribeiro, 2019).

Historically, the incidence of ocular trauma has shown significant variations, with an increase in severe injuries between 1990 and 2010, especially in conflict areas and intensive industries (Cheung *et al.*, 2014). In Brazil, ocular traumas are common causes of emergency care, with a prevalence of diseases such as conjunctivitis and corneal abrasion (Guevara, 2024). Recently, awareness campaigns and improvements in medical care have contributed to a reduction in the incidence rate of severe traumas (Cheung *et al.*, 2014).

Ocular trauma should be prioritized in emergency care as it can lead to poor prognosis, such as total vision loss. However, most physicians attending these situations are not specialists (Jayme *et al.*, 2023). A survey pointed out that a general practitioner should be able to resolve 69% of ophthalmic emergency cases, but for good effectiveness, this number should be above 70%. Unfortunately, most hospitals present percentages below this average. About 93% of on-call physicians do not feel confident in handling ophthalmic patients (Jayme *et al.*, 2023).

Risk factors for ocular traumas include exposure to hazardous work environments, such as construction and agriculture, especially among adult men (Guevara, 2024; Cheung *et al.*, 2014). In childhood and adolescence, inadequate care increases susceptibility to traumas (Guevara, 2024). Additionally, behavioral factors, such as not using protective equipment, and genetic predispositions are also significant (Cheung *et al.*, 2014). Falls and physical assaults are the main causes of ocular traumas, commonly involving direct impact with objects and penetrating injuries.

The use of Personal Protective Equipment (PPE), combined with immediate medical attention in case of an accident, is crucial for a better patient prognosis. Statistical data reveal that 58% of patients attended in ophthalmic emergencies are men, with a high morbidity rate, often resulting in partial or total vision loss (Guevara, 2024; Cheung *et al.*, 2014). In a study conducted in 2016-2017, 6,483 patients were attended in the ophthalmic emergency unit, indicating the need for improvements in initial care, frequently provided by non-specialist physicians (Guevara, 2024). The mortality rate is low, but a rapid and effective medical response is crucial for survival and reduction of severe complications (Cheung *et al.*, 2014).

DIAGNOSIS

Early diagnosis in ocular trauma situations is extremely important because, in addition to improving the prognosis and relieving the discomfort caused by the trauma, quick identification can prevent serious complications and permanent vision damage. Some conditions are diagnosed only with imaging exams, however, any initial conduct in cases of ocular trauma must begin with a complete clinical evaluation, including visual acuity, tests for the presence of a relative afferent pupillary defect, evaluation of the anterior segment, and when possible, evaluation of the posterior segment of the eyeball (Balakrishnan *et al.*, 2020).

The signs and symptoms of ocular trauma vary according to the mechanism of the injury, highlighting the importance of evaluating the time elapsed since the trauma, and whether the injury was penetrating or resulted from a chemical burn. In the latter case, it is essential to obtain a detailed history, including the specific type of chemical compound involved, the time between exposure and irrigation, the duration and type of irrigation performed, and whether there was any eye protection, as these factors determine the severity, prognosis, and treatment (Logothetis; Leikin and Patrianakos, 2014).

In the evaluation of patients with corneal abrasion, the focus should be on evidence of penetrating trauma, decreased visual acuity, and signs of infection. These patients generally present with acute pain, photophobia, tearing, discomfort when blinking, and a foreign body sensation. In cases of hyphema, understanding the force, speed, type, and direction of the injury is crucial to facilitate more effective treatment. The clinic of traumatic iritis tends to include dull or aching pain, photophobia, decreased vision, and tearing, occurring within three days after the trauma. There may also be changes in intraocular pressure, mydriasis, miosis, conjunctival injection around the limbus, decreased vision, and the presence of floaters (Logothetis; Leikin and Patrianakos, 2014).

Patients with hyphema should pay attention to the use of anticoagulants such as aspirin, warfarin, clopidogrel, or non-steroidal anti-inflammatory drugs (NSAIDs). Additionally, the patient should be questioned about the presence of sickle cell disease and coagulopathies, as these conditions can influence the management and prognosis of ocular trauma (Logothetis; Leikin and Patrianakos, 2014). It is important to note that optic nerve injury may not be detected in the context of bilateral optic nerve injuries. Non-reactive pupils, in cases of traumatic brain injury, coma, or elevated intracranial pressure, make it difficult to assess a relative afferent pupillary defect (Balakrishnan *et al.*, 2020). If there is concern about a vascular injury affecting the orbit, such as a carotid-cavernous fistula, a computed tomography angiography (CTA) of the head may be indicated (Balakrishnan *et al.*, 2020).

The initial assessment of ocular trauma is based on a thorough evaluation of the patient, with special attention to the face, looking for signs of superficial wounds, penetrating

injuries, avulsed tissues, or absence thereof. The physical examination should include an assessment of the eyes, eyelids, lacrimal system, and orbit (Ko *et al.*, 2021).

For open globe traumas, the initial examination should include an evaluation of visual acuity, inspection of the anterior chamber, performing the Seidel test (when indicated), and a detailed visual inspection that can assist in deciding to perform an examination under anesthesia. Other diagnostic modalities that may be necessary include the use of computed tomography (CT). In the evaluation of patients with closed globe injury, it is essential first to rule out an open globe injury. As in open globe injuries, a detailed ocular examination, including visual acuity verification, is crucial. Although the slit lamp generally offers the best details, in patients who cannot use it, alternative methods should be considered. In young children, a portable slit lamp may be used; however, to avoid the lower part of the device pressing against the child's chest, the device can be turned upside down (Miller, 2017).

The sensitivity of orbital radiographs for fractures varies between 64% and 78%, being mainly used for detecting metallic foreign bodies in the orbit (Balakrishnan *et al.*, 2020). Non-contrast CT of the orbits is preferred for initial investigation, as it is widely available, offers high resolution, and can be performed quickly (Balakrishnan *et al.*, 2020). CT is widely used in orbital trauma cases, and 1.5 to 2 mm cuts should be made in axial and coronal planes (Gomes; Castro e Silva and Ribeiro, 2019).

B-scan ultrasonography is especially useful in detecting intraorbital and intraocular damage. Although CT is superior to ultrasound for locating foreign bodies, ultrasonography is still employed in cases of retained intraocular foreign bodies, posterior segment evaluation in closed globe injuries with opacification, detection of hidden perforations in open globe injuries, iatrogenic globe injuries, and sequelae of acute penetrating trauma (Mahesh *et al.*, 2019).

X-rays are mainly used to diagnose fractures and locate foreign bodies (Gomes; Castro e Silva; Ribeiro, 2019). The full-field electroretinogram (ERG) is indicated when the patient's eyes have no light perception, being crucial for assessing the vitality of photoreceptor function. On the other hand, the multifocal ERG detects areas of the retina affected by trauma (Gomes; Castro e Silva; Ribeiro, 2019).

Magnetic resonance imaging (MRI) is not recommended for the initial evaluation of trauma and is contraindicated in cases of suspected metallic foreign bodies. However, MRI offers superior delineation of intraorbital and orbitocranial hemorrhages associated with foreign bodies and hematomas (Mahesh *et al.*, 2019). Fundus autofluorescence is used to assess the integrity of the retinal pigment epithelium in closed traumas, being a useful alternative when fluorescein fundus angiography is contraindicated. Choroidal ruptures can be visualized in FAF, and in cases of subretinal hemorrhage and Purtscher's retinopathy, the image appears hypoautofluorescent (Mahesh *et al.*, 2019). Additionally, spectral-domain optical coherence tomography (SD-OCT) can identify the location of choroidal rupture and subretinal hemorrhage in closed traumas (Mahesh *et al.*, 2019). In cases of ocular chemical burns, the diagnosis is predominantly clinical (Logothetis; Leikin; Patrianakos, 2014).

Currently, advanced techniques have significantly improved the diagnosis of ocular traumas. Optical Coherence Tomography (SD-OCT) and Fundus Autofluorescence (FAF) are useful for assessing the extent and severity of post-traumatic retinal damage, providing crucial information about the patient's visual prognosis. These non-invasive exams allow the evaluation of changes in the posterior segment of the eye, as well as the metabolic activity of the retinal pigment epithelium cells and anatomical changes in the outer layers of the retina (Mahesh *et al.,* 2019). Computed tomography (CT) and ocular ultrasonography are essential in evaluating open globe injuries and detecting intraocular foreign bodies, with CT correctly identifying up to 94.9% of cases and being preferred for orbital fractures, bone injuries, and acute trauma evaluation due to its speed and high resolution (Balakrishnan *et al*., 2020). B-scan ultrasonography, in turn, is safe for use in patients with metallic foreign bodies and effective in evaluating posterior segment injuries, retinal and choroidal detachments, and sequelae of acute penetrating traumas (Gomes; Castro e Silva; Ribeiro, 2019).

Ultrasonic Biomicroscopy (UBM) is highly effective in detecting anterior segment injuries, such as hemorrhages and lens dislocations, offering high-resolution images and improving diagnostic accuracy (Mahesh *et al.,* 2019). Advanced magnetic resonance imaging (MRI), despite being contraindicated in cases of magnetic foreign bodies, is useful for detailed visualization of extraocular muscles, optic nerve, and orbital structures without exposure to ionizing radiation. MRI provides excellent differentiation of soft tissue types, allowing early detection of injuries that previously could only be identified at advanced stages or through invasive techniques (Mahesh *et al*., 2019). In ocular chemical burns, the diagnosis is predominantly clinical, emphasizing the importance of the patient's history and detailed physical examination (Logothetis; Leikin and Patrianakos, 2014).

TREATMENT

The initial approach for any type of ocular trauma begins with the assessment and stabilization of the patient, followed by a detailed examination of the injured eye (Gomes; Castro e Silva and Ribeiro, 2019). In cases of closed trauma, such as contusions or corneal abrasions, therapy includes the use of antibiotic eye drops to prevent infections and anti-inflammatory eye drops to reduce inflammation (Miller, 2017). Oral analgesics may also be prescribed to relieve pain (Gomes; Castro e Silva and Ribeiro, 2019). In cases of corneal abrasion, it is important to avoid the use of contact lenses until the injury is completely healed, which usually occurs within 24 to 48 hours (Logothetis; Leikin; Patrianakos, 2014; Miller, 2017).

For penetrating or open traumas, management is more complex and often requires surgical intervention (Gomes; Castro e Silva and Ribeiro, 2019). Penetrating globe wounds require immediate surgical repair to prevent the loss of intraocular contents and

infection (Miller, 2017). The procedure includes suturing the wound with non-absorbable material, such as 8-0 sutures for the sclera and 10-0 for the cornea (Logothetis; Leikin and Patrianakos, 2014). In cases of intraocular foreign bodies, surgical removal is mandatory to avoid complications such as endophthalmitis and ocular toxicity (Logothetis; Leikin and Patrianakos, 2014; Miller, 2017).

Chemical traumas, including burns caused by acids or alkalis, require immediate and abundant irrigation with saline solution or clean water to neutralize the chemical agent (Logothetis; Leikin and Patrianakos, 2014). After irrigation, the use of antibiotic and steroid eye drops is common to prevent infections and reduce inflammation (Gomes; Castro e Silva and Ribeiro, 2019). Irrigation should continue until the pH of the ocular surface is normalized (Logothetis; Leikin and Patrianakos, 2014). In severe cases, debridement of necrotic tissue and the application of therapeutic contact lenses may be necessary to promote healing (Logothetis; Leikin and Patrianakos, 2014; Gomes; Castro e Silva and Ribeiro, 2019).

In cases of hyphema, which is the accumulation of blood in the anterior chamber of the eye, treatment includes rest, elevation of the head to 30-45 degrees to facilitate blood sedimentation, and administration of cycloplegics and topical corticosteroids (Miller, 2017). Intraocular pressure should be closely monitored, and in cases of persistent elevated pressure, the use of beta-blockers or surgery to remove the accumulated blood may be necessary (Gomes; Castro e Silva and Ribeiro, 2019; Miller, 2017).

Traumatic iritis, which is the inflammation of the iris usually caused by blunt trauma, is treated with cycloplegic eye drops to relieve pain and prevent adhesions between the iris and the lens, along with topical corticosteroids to reduce inflammation (Miller, 2017). Continuous follow-up by an ophthalmologist is crucial to monitor possible complications such as the development of glaucoma or retinal detachment (Logothetis; Leikin and Patrianakos, 2014; Miller, 2017).

Chemical burns are one of the most common causes of ocular trauma and require immediate intervention. Instant irrigation is used to restore the pH to normal levels. Many authors do not recommend the use of contact lens-based devices to provide irrigation to the ocular surface, as they can cause more damage if used by untrained individuals and may not adequately irrigate the conjunctival fornices, impairing the patient's prognosis (Miller, 2017; Logothetis; Leikin and Patrianakos, 2014).

Corneal abrasions require appropriate investigation and thorough treatment. The patient's pain should be relieved with oral or topical anti-inflammatories. A recent study evidenced the use of diluted topical proparacaine for symptom relief, but its use is not recommended due to the delay in healing the injuries (Logothetis; Leikina and Patrianakos, 2014).

Pediatric ocular trauma is one of the main causes of monocular blindness worldwide, stemming from various etiologies, including physical abuse. Recent studies show that after the first ocular trauma, there is a threefold increase in the chance of a new trauma. In this

sense, the use of classification systems, such as the Birmingham Eye Injury Terminology System (BETTS) and the Ocular Trauma Score (OTS), aids in decision-making and allows accurate prognosis, avoiding underestimation of injuries (Guevara, 2024).

Management of orbital trauma has also undergone modifications. It is essential to request orbital and maxillofacial imaging in computed tomography (CT) for detailed evaluation of the orbits and early detection of injuries (Balakrishnan *et al.*, 2020). In minimally or non-displaced orbital rim fractures, surgery may be avoided. For midface fractures, less invasive approaches offer better appearance and reduce complications. Orbital floor injuries are preferably treated through transconjunctival incision, minimizing the risk of entropion or ectropion and avoiding skin incisions. The placement of implants in these fractures can be assisted by the use of intraoperative CT (Lozada; Cleveland and Smith, 2019).

Soft tissue trauma requires prompt repairs for better postoperative outcomes. Contaminated wounds should be irrigated with sterile saline solution, and there is no contraindication for immediate repair. Healing by secondary intention is not recommended in areas where scars may cause deformities or movement limitations, such as the upper eyelid crease or lower eyelid. The presence of foreign bodies indicates imaging exams, with CT being the examination of choice for penetrating injuries and traumas with unknown mechanisms, with mandatory removal of the object in a surgical center (Ko *et al.*, 2021).

The development of glaucoma after ocular trauma is a consequence evidenced in several studies. In chemical injury, intraocular pressure (IOP) can be controlled in the acute phase with topical glaucoma medications. There is no consensus regarding the contraindication of using prostaglandin analogs and pilocarpine in trauma. If IOP increases after medication option, surgical approach is necessary. Prolonged use of steroids after traumatic iritis can lead to IOP elevation, controlled with antiglaucoma agents, except prostaglandin analogs in cases of uveitis. In hyphema, the same drug therapy is indicated, with surgical intervention performed in young and healthy individuals with normal optic nerve when IOP is >50 mmHg for more than 5 days, >45 mmHg for more than 1 week, or >35 mmHg for more than 2 weeks. In the treatment of phacomorphic glaucoma, laser peripheral iridotomy (LPI) before surgical intervention benefits all individuals, preventing an acute attack and quickly controlling IOP (Razeghinejad *et al.*, 2020).

According to the World Health Organization (WHO), 90% of people with visual impairment live in low-income countries. About 28% of people with moderate to severe visual impairment are of working age, significantly impacting their professional and economic lives. Approximately 80% of visual impairment cases could be avoided or treated, but access to prevention, education, treatment, and rehabilitation services is very limited (Guevara, 2024).

Ophthalmic emergencies can lead to vision loss, making it crucial to recognize and communicate ophthalmic findings to prevent irreversible visual damage. An initial comprehensive examination, including visual acuity, intraocular pressure, and pupil evaluation, is essential. Additionally, referral for continuous ophthalmic follow-up is necessary

to rule out complications and ensure proper care after initial treatment (Logothetis; Leikin and Patrianakos, 2014).

Ocular trauma can cause elevated intraocular pressure (IOP), making it essential to understand and identify the causes of this elevation in each case to choose appropriate therapeutic approaches. Initial IOP measurement can provide critical information about the need for surgical intervention (Razeghinejad *et al.*, 2020).

According to Miller (2017), ocular traumas in children can lead to vision loss. Closed globe injuries are treatable on an outpatient basis and generally have better visual outcomes. In contrast, open globe injuries have a poorer visual prognosis, often requiring surgical intervention due to delays in initial treatment.

REFERENCES

BALAKRISHNAN, Sudheer, *et al.* Imaging review of ocular and optic nerve trauma. **Emergency Radiology**, v. 27, p. 75-85, 2020.

CHEUNG, Cindy A., *et al.* Hospital-based ocular emergencies: epidemiology, treatment, and visual outcomes. **The American Journal of Emergency Medicine**, v. 32, n. 3, p. 221-224, 2014.

GOMES, Mariana Studart Mendonça; CASTRO E SILVA, Sarah Rubia Sales de; RIBEIRO, João Crispim Moraes Lima. Trauma ocular: revisão das condutas na emergência. **Brazilian Journal of Health Review**, v. 2, n. 5, p. 4537-4548, 2019.

GUEVARA, José Alberto Garcés. Trauma ocular pediátrico y repercusiones visuales. Revisión sistemática. **Revista Información Científica**, v. 103, 2024.

JAYME, Brenda Cavalieri, *et al*. Principais ocorrências na emergência oftalmológica com enfoque em traumas oculares: uma revisão integrativa. **Research, Society and Development**, v. 12, n. 1, p. e14912139765-e14912139765, 2023.

KO, Audrey C.; SATTERFIELD, Kellie R.; KORN, Bobby S.; KIKKAWA, Don O. Eyelid and periorbital soft tissue trauma. **Oral and Maxillofacial Surgery Clinics**, v. 33, n. 3, p. 317-328, 2021.

LOGOTHETIS, Hercules D.; LEIKIN, Scott M.; PATRIANAKOS, Thomas. Management of anterior segment trauma. **Disease-a-Month**, v. 60, n. 6, p. 247-253, 2014.

LOZADA, Kirkland N.; CLEVELAND, Patrick W.; SMITH, Jesse E. Orbital trauma. In: Seminars in plastic surgery. **Thieme Medical Publishers**, p. 106-113, 2019.

MAHESH, G., *et al.* Imaging in posterior segment ocular trauma. **Kerala Journal of Ophthalmology**, v. 31, n. 2, p. 92-101, 2019.

MILLER, Kyle E. Pediatric ocular trauma: an update. **Current Ophthalmology Reports**, v. 5, p. 107-113, 2017.

POUCHAIN, Ernest Cavalcante, *et al.* Alterações funcionais como consequências de traumatismo orbitário: revisão da literatura. **ARCHIVES OF HEALTH INVESTIGATION**, v. 9, n. 5, p. 464-467, 2020.

RAZEGHINEJAD, Reza, *et al.* Pathophysiology and management of glaucoma and ocular hypertension related to trauma. **Survey of Ophthalmology**, v. 65, n. 5, p. 530-547, 2020.

Chapter 23

TRAUMATIC BRAIN INJURY

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CHAPTER 23

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Traumatic brain injury (TBI) is a critical medical condition often resulting from direct impacts or acceleration-deceleration forces, which can cause temporary or permanent damage to the brain. It is one of the leading causes of morbidity and mortality worldwide, especially among young and adult individuals. Due to its multifaceted nature, TBI can lead to a wide range of neurological, cognitive, and behavioral deficits, significantly affecting the quality of life of patients (McGinn; Povlishock, 2016).

Within the spectrum of medical emergencies, TBI represents a significant challenge for both diagnosis and treatment. Studies indicate that hemorrhagic progression in the pericontusional zones of the brain, initially attributed to coagulopathy, involves several other causal factors. Additionally, the severity of brain contusions is closely related to the size, location, and potential for bilateral involvement of the brain (McGinn; Povlishock, 2016).

TBI is the most common cause of death and disability in individuals under 40 years old in the United Kingdom. In low- and middle-income countries, mortality and morbidity rates are even higher (Khellaf; Khan and Helmy, 2019). Globally, it is estimated that millions of cases of TBI occur each year, with a substantial impact on public health and healthcare systems.

Demographic data on TBI show a higher prevalence among males, particularly in younger ages, due to factors such as traffic accidents, falls, and sports activities. The incidence of TBI varies geographically, being higher in regions with poor safety infrastructure and less access to specialized medical care (Khellaf; Khan and Helmy, 2019).

Historically, the approach to TBI has evolved significantly with the advancement of imaging technologies and neurological monitoring. The implementation of specialized neurointensive care and legislation on the use of protective equipment, such as seat belts and helmets, have contributed to reducing the incidence and improving outcomes in TBI patients (Khellaf; Khan and Helmy, 2019).

Risk factors for TBI include young age, male sex, participation in contact sports, traffic accidents, falls, and interpersonal violence. Additionally, exposure to hazardous work environments and the absence of adequate safety measures significantly increase the risk of TBI. Statistics indicate that patients with severe TBI have a high hospital mortality rate. Studies show that accurately defining the severity of TBI is crucial for the uniformity and precision in patient classification, improving clinical practice and epidemiological research (Savitsky *et al.*, 2016). Prevention strategies for TBI include the use of protective equipment, awareness campaigns on traffic and workplace safety, and strengthening safety regulations. Early screening programs and rapid response protocols are essential for the effective identification and treatment of TBI, minimizing long-term impact (Dennis *et al.*, 2022).

EPIDEMIOLOGY

Traumatic brain injury (TBI) is a severe public health issue occurring in various contexts worldwide, affecting a broad age range and showing significant global prevalence. The condition is often classified into degrees of severity (mild, moderate, and severe) based on the Glasgow Coma Scale, with most reported cases considered mild, representing about 75% to 90% of cases (Haarbauer-Krupa *et al.*, 2021; Toccalino; Colantonio; Chan, 2021; Williams *et al.*, 2020).

Historically, TBI was more prevalent among the young population, particularly due to traffic accidents and high-impact sports activities. However, with the increasing aging of the global population, there has been a significant shift, with a rise in the incidence of TBI among the elderly, especially in developed countries. This demographic change requires new approaches and techniques for the appropriate management of TBI in the elderly, reflecting the need for the development of specific prevention and treatment strategies (Giner *et al.*, 2022; Pugh *et al.*, 2020; Brazinova *et al.*, 2020).

The main risk factors for TBI include falls from a standing height, injuries during sports activities, and violence, such as fights and assaults, in addition to traffic accidents. Vulnerable populations, such as the elderly, people with neurodegenerative disorders (Alzheimer›s disease and Parkinson›s disease), individuals experiencing intimate partner violence, and high-impact sports athletes, are more susceptible to TBI. Additionally, genetic factors and pre-existing medical conditions, such as neurodegenerative diseases, also significantly contribute to the risk of developing TBI (Williams *et al.*, 2018; Toccalino; Colantonio and Chan, 2021; Mollayeva; Mollayev and Colantonio, 2018; Giner *et al.*, 2020; Baggiani *et al.*, 2020).

Globally, it is estimated that approximately 69 million people suffer from TBI each year. The distribution of TBI shows a male predominance, with a ratio of 16:1 between men and women suffering severe TBI. In the United States, recent studies indicate that TBI is one of the most prevalent causes of emergency room visits, totaling about 2.87 million cases, with the main causes being collisions with objects, falls, and motor vehicle accidents (Toccalino; Colantonio; Chan, 2021; Haarbauer-Krupa *et al.*, 2021; Mollayeva; Mollayeva and Colantonio, 2018; Kennedy *et al.*, 2020; Majdan *et al.*, 2020).

DIAGNOSIS

The pathophysiology of traumatic brain injury (TBI) is not just an acute event but also a progressive and delayed neurodegenerative process composed of multiple, parallel, interactive, and interdependent cascades of biological reactions at the tissue, cellular, and subcellular levels. Axons are particularly vulnerable to physical trauma, and axonal injury is a common occurrence in both focal and diffuse brain trauma and can be found in TBI regardless of its severity. Not only are neurons at risk of injury, but also astroglial cells and oligodendrocytes (Wang *et al.*, 2018).

A comprehensive understanding of the pathological processes at the cellular and subcellular levels is fundamental for developing precise diagnostic and prognostic molecular biomarkers for TBI (Beard; Meaney; Issadore, 2020; Wang et al., 2018; Najen et al., 2018). The absence of validated diagnostic biomarkers leads to a reliance on subjective clinical symptoms for the diagnosis of TBI. Neuroimaging biomarkers are clinically established for moderate to severe TBI, but other imaging modalities are still at recommendation levels II-III (Wilde *et al.*, 2022).

Computed tomography (CT) scans are crucial for identifying life-threatening conditions post-TBI, while magnetic resonance imaging (MRI) provides detailed anatomical information for diagnostic clarity (Wilde *et al.*, 2022). CT, the initial modality used during TBI diagnosis, only assesses macroscopic anatomical changes characteristic of severe TBI, such as hemorrhages and brain lesions, but does not evaluate other features like inflammation, gliosis, and diffuse axonal injury (Beard; Meaney and Issadore, 2020; Wang et al., 2018). MRI can be used to assess regions of increased brain activity, altered cerebral blood flow, axonal, and microvascular pathology, but its high cost and inaccessibility limit its use for repeated monitoring of TBI progression (Beard; Meaney and Issadore, 2020). In selected cases, MRI can also provide important information due to its better tissue contrast and increased sensitivity compared to CT (Albano *et al.*, 2023).

Electroencephalogram (EEG) and imaging exams are standard clinical measures for TBI assessment. Molecular biomarkers derived from cerebrospinal fluid (CSF) or serum biopsy overcome many limitations associated with these measures (Najen et al., 2018) and have been used to evaluate inflammation, oxidative stress, excitotoxicity, and other pathophysiological mechanisms occurring within days to weeks after the injury (Beard; Meaney and Issadore, 2020; Wang *et al.*, 2018; Najen *et al.*, 2018).

As biomarkers indicative of neuronal cellular injury, Neuron-Specific Enolase (NSE), a homodimer found in mature neurons and neuroendocrine cells, and Ubiquitin C-terminal Hydrolase-L1 (UCH-L1), a neuronal cytosolic protein, are evaluated (Wang et al., 2018; Najen et al., 2018). Elevations of NSE have been observed in the blood compartment (Wang et al., 2018) and UCH-L1 in the cerebrospinal fluid and serum of patients with severe TBI (Wang *et al.*, 2018; Najen *et al.*, 2018). The general concept is that injured neurons release such molecules into the interstitial fluid, where they gain access to the CSF and systemic circulation (Najen et al., 2018). A major disadvantage of using NSE as a specific marker for TBI is its abundance in red blood cells, requiring consideration of hemolytic processes in the blood measurement of NSE (Wang *et al.*, 2018). UCH-L1 is not specific to the central nervous system (CNS) and is expressed by peripheral nervous system cells, some tumor cells, endocrine system cells, and smooth muscle cells (Najen *et al.*, 2018).

The S100B protein, a calcium-binding astroglial protein (Wang et al., 2018), and glial fibrillary acidic protein (GFAP) have been analyzed as astroglial biomarkers. S100B is also released by adipose tissue and cardiac/skeletal muscles, and its levels are elevated in orthopedic trauma without TBI. Nevertheless, it is a sensitive marker as a predictor of CT abnormalities and the development of post-concussion syndromes. GFAP biomarker levels are elevated within 3 to 34 hours in CSF and serum after severe TBI and in serum samples after moderate TBI, with this increase being trauma severity-dependent (Wang *et al.*, 2018; Najen *et al.*, 2018).

Neurofilament (NF) proteins and myelin basic protein (MBP) are markers of late axonal injury and demyelination (Wang *et al.*, 2018). NFs exist as bundles known as

neurofibrils, which are an important component of the cytoskeleton, primarily functioning to provide structural support to the axon. They can be dissociated from the cytoskeleton into the cytosol or possibly the extracellular fluid if cell membrane integrity is compromised (Wang *et al.*, 2018). MBP degradation results from axon and myelin sheath deterioration and can be released into biofluids (CSF and/or serum) after TBI (Wang *et al.*, 2018).

MicroRNAs (miRNAs) have been evaluated as emerging biomarkers in TBI diagnosis based on their roles in regulating various cellular functions in the brain. miRNA-targeted genes are involved in a wide range of processes such as neurogenesis and brain development, differentiation of neural cells like oligodendrocytes, myelination and axon guidance, regulation of synaptic plasticity, and inflammatory genes (Albano *et al.*, 2023; Wang *et al.*, 2018; Najen *et al.*, 2018). These biomarkers can be detected early in the blood, establishing themselves as a rapid diagnostic tool essential in emergency and urgent care contexts. This early detection capability is vital for initiating effective treatment and mitigating severe complications (Albano *et al.*, 2023). miRNAs are short, non-coding regulatory RNA molecules composed of 20 to 24 nucleotides usually located within introns, playing important roles in regulating gene/protein expression. Several microRNAs have indeed been identified at elevated levels in the biofluids (CSF, serum, or plasma) of TBI patients (Wang *et al.*, 2018; Najen *et al*, 2018), such as miR-16 and miR-92a (Wang *et al.*, 2018; Najen *et al.*, 2018) in moderate TBI patients, and miR-93, miR-191 (Wang *et al.*, 2018; Najen *et al.*, 2018), and miR-499 (Najen et al., 2018) in the serum of patients with mild, moderate, and severe TBI. The levels of all three miRNAs were related to injury severity and clinical outcomes several months later (Wang *et al.*, 2018; Najen *et al.*, 2018). The downregulation of miR-425-5p and miR-502 shortly after injury characterized moderate TBI patients, while the upregulation of miR-21 and miR-335 was observed in the serum of patients after severe TBI (Najen *et al.*, 2018).

Notably, miRNA sample collection involves non-invasive methods, which is advantageous in emergency settings where patients may be in debilitating or critical conditions. The technology for detecting miRNAs, including microarrays, next-generation sequencing (NGS), and quantitative real-time PCR (qRT-PCR), can be adapted depending on the need for broad screening or targeted analysis of specific miRNAs. Additionally, the use of bioinformatics systems to identify target genes of dysregulated miRNAs and their related signaling pathways could also link severe TBI with neurodegenerative conditions, acting as a prognostic marker for this condition (Albano *et al.*, 2023).

Exosomes (EVs) are membranous vesicles released from all types of neural cells, varying in size and origin, and possessing specific surface markers, RNA, and proteins (Beard; Meaney and Issadore, 2020). Studies on the use of exosomes as diagnostic biomarkers for TBI have focused on traditionally evaluated proteins, such as UCHL1, Tau, and β-amyloid (Beard; Meaney and Issadore, 2020). Exosomes derived from neurofunctional proteins, such as UCHL1 and occludin, showed transient elevations in their levels after

the acute event, while elevated levels of exosomes composed of Tau and β-amyloid were exhibited in both acute and chronic events (Beard; Meaney and Issadore, 2020).

Most biomarker studies for TBI lack validation in large cohorts and do not meet Level 1 Evidence standards, hindering their clinical use (Wilde *et al.*, 2022). However, diagnostic biomarkers have the potential to differentiate TBI endophenotypes, aiding in identifying patients who may benefit most from specific interventions. Combining digital biomarkers with neuroimaging and biofluid markers would enhance TBI assessment and patient stratification for better clinical decision-making, given the current limitations of these methods due to the heterogeneity of injuries. Predictive biomarkers offer insights into treatment responses and clinical outcomes (Wilde *et al.*, 2022). The use of machine learning algorithms to analyze multimodal biomarker data could provide a comprehensive understanding of TBI pathophysiology and patient outcomes.

TREATMENT

The primary goal in the treatment of Traumatic Brain Injury (TBI) is to minimize or prevent the progression to secondary injury, primarily ischemia and intracranial hypertension, highlighting the need for early intervention. Thus, patient management strategies aim to reduce edema and intracranial pressure, as well as to preserve cerebral perfusion and oxygen delivery to brain tissue (Jinadasa; Boone, 2016).

The treatment plan varies according to the severity of the TBI, classified as mild, moderate, or severe using the Glasgow Coma Scale. However, regardless of the severity, the therapeutic approach is always focused on preventing possible secondary injury. In the initial management, hemodynamic stabilization, monitoring and maintenance of intracranial pressure and cerebral perfusion, ventilatory and oxygenation support if necessary, administration of hyperosmolar saline solution and/or sedatives, seizure prophylaxis, and nutritional support form the basis of patient care. In more severe cases, surgical options such as decompressive craniotomy or cerebrospinal fluid drainage via ventricular drain are emphasized. Additionally, therapeutic adjustments are made as needed and based on the patient›s individualized response (Yan *et al.*, 2024).

Another important aspect of TBI treatment is providing information and guidance to both the patient and their family regarding medical follow-up after the event. Even in mild cases, it is essential that the patient and/or their companion be advised to return to the healthcare service if warning signs or severe symptoms, such as altered consciousness and seizures, occur. Therefore, implementing educational strategies by the healthcare team is crucial in preventing and managing post-TBI sequelae (Seabury *et al.*, 2018).

Severely injured patients require immediate care and rapid stabilization to prevent worsening. Monitoring and maintaining systemic blood pressure is critical, with the need to recognize both hypotension and hypertension. A systolic pressure of up to 100 mmHg is

recommended for patients aged 49 to 69 years, and up to 110 mmHg for patients aged 15 to 49 years or over 70 years. Intravenous saline solutions should be administered as needed. After hemodynamic normalization, an urgent non-contrast head computed tomography (CT) scan should be performed, as it is the standard initial examination for moderate to severe TBI. In children, radiation exposure should be considered before deciding to obtain a CT scan (Yan *et al.*, 2024; Jinadasa *et al.*, 2016).

Intracranial pressure (ICP) monitoring should be performed via an intraventricular catheter, considered the gold standard for being the most accurate and measuring global ICP. Guidelines recommend maintaining ICP below 22 mmHg and a target cerebral perfusion pressure (CPP) between 60 to 70 mmHg. Reduction of ICP to adequate levels is achieved through sedation, induced hyperventilation, hyperosmolar therapy (use of mannitol), hypothermia, and appropriate surgical treatment (Yan *et al.*, 2024; Jinadasa *et al.*, 2016).

Hyperosmolar therapy or osmotherapy is administered when sedation, intubation, and postural repositioning are not effective in reducing ICP. Osmotherapy is often administered with mannitol at the standard dose of 0.25 - 1g/Kg every 6 hours to reduce ICP (Yan *et al.*, 2024; Jinadasa *et al.*, 2016).

Mechanical ventilation is frequently used, and guidelines recommend hyperventilation as a temporary measure to reduce ICP, which should be avoided in the first 24 hours and used with moderation and for a limited time (Yan *et al.*, 2024; Jinadasa *et al.*, 2016).

TBI patients with elevated levels of fibrinogen degradation products may benefit from early administration, within 3 hours, of tranexamic acid (TXA) to reduce the likelihood of death due to extracranial bleeding (Yan *et al.*, 2024; Jinadasa *et al.*, 2016).

Hypothermia has been used as a prophylactic neuroprotector, serving as a resource to control increased ICP by reducing cerebral blood flow and volume (Yan *et al.*, 2024; Jinadasa *et al.*, 2016). Studies indicate that treating fever can decrease brain damage in patients with severe brain injuries and reduce shivering through therapeutic interventions such as buspirone, meperidine, or neuromuscular blocking agents.

After implementing general measures, the surgical resection of lesion masses and CSF drainage should be considered. According to the 2017 guidelines for severe TBI, initial surgical evacuation of an epidural hematoma is recommended if the patient has a Glasgow Coma Scale (GCS) score less than 9, clot thickness greater than 15mm, and midline shift greater than 5mm, or a focal neurological deficit. Additionally, surgical evacuation can also be considered if the subdural hematoma (SDH) is greater than 1 cm, with a midline shift greater than or equal to 5mm, GCS less than 8, and ICP greater than 20 mmHg or rapid neurological decline. Surgery for eligible patients shows significant mortality benefit if evacuation is performed within less than 4 hours (Yan *et al.*, 2024).

Decompressive craniectomy is a surgical method that can be used as a treatment option for severe refractory cases of intracranial hypertension. This method involves removing part of the skull where the dura mater is opened to increase the volume of the

cranial cavity and thereby reduce ICP. While effective, it includes risks such as wound infection, meningitis, brain abscess, CSF leakage, hematoma, and cerebral infarction (Jinadasa *et al.*, 2016).

Moderate to severe TBI is often associated with physical and mental sequelae or disabilities. These deficits can be challenging to detect due to their silent epidemiology. Sequelae can range from mild deficits to comatose states and have significant implications for both short-term management and long-term care of individuals with TBI. Delirium after TBI is one of the most frequent manifestations, typically lasting an average of 43 days in patients with severe TBI (de Guzman *et al.*, 2017).

The standard treatment consists of addressing other contributing medical factors such as infection, dehydration, electrolyte disturbances, severe anemia, hypoxia, and hypotension, among others. A review of the patient›s medications should be conducted to eliminate those that may contribute to delirium, such as benzodiazepines, highly anticholinergic drugs, and excess or inappropriate administration of opioids. Psychosocial measures are essential for this type of treatment, including sleep-wake cycle regulation, reorientation, sensory aids, and early mobilization with physical therapy and getting out of bed. Antipsychotics are used for delirium in the general hospital and ICU, and anticonvulsants are also used to treat different neuropsychiatric sequelae, particularly if they present with seizure disorders, mood lability, mania, impulsivity, and aggression (de Guzman *et al.*, 2017).

In addition to the common therapies mentioned above, new medications are being tested to enhance TBI treatment, such as Amantadine Hydrochloride, a drug traditionally used to control dyskinesia in Parkinson›s disease and for prophylaxis against certain viruses. Amantadine acts as an NMDA receptor antagonist and dopaminergic agonist, thus being useful in controlling cognitive deficits observed in TBI due to dopaminergic and glutamatergic dysregulation. The medication was well-tolerated and showed medium-term cognitive benefits; however, its long-term effects have not been fully elucidated, and its efficacy in cognitive recovery was only proven for four weeks of treatment, with a loss of effectiveness by the sixth week. Therefore, further studies on the application of Amantadine in controlling post-TBI cognitive deficits are essential to confirm the reliability of this drug (Loggini *et al.*, 2020).

Non-invasive monitoring methods are also being developed, such as Near-Infrared Spectroscopy (NIRS), which assesses cerebral perfusion by analyzing the absorption of infrared light by tissue. This works because, between wavelengths of 700 nm and 1000 nm, the absorption of radiation by oxygenated and deoxygenated hemoglobins is maximized, while that of other components is minimized. Thus, it is possible to obtain information on the supply and consumption of oxygen by brain tissue, enabling non-invasive monitoring of patients who have suffered TBI (Roldán; Kyriacou, 2021).

Currently, the methods used to monitor patients are more invasive and complex, such as subdural, parenchymal, or intraventricular catheters for monitoring intracranial pressure

(ICP), as well as imaging exams (computed tomography and magnetic resonance imaging). Since these methods can require more time to perform in certain scenarios, combining them with less invasive forms like NIRS, which can be used both in hospital beds and ambulances, can be beneficial for the early detection of changes in pressure and cerebral perfusion (Roldán; Kyriacou, 2021).

REFERENCES

ALBANO, Giuseppe Davide, *et al.* An Overview on the Use of miRNAs as Possible Forensic Biomarkers for the Diagnosis of Traumatic Brain Injury. **International Journal of Molecular Sciences**, v. 24, n. 7, p. 6503, 2023.

BAGGIANI, Marta; GUGLIELMI, Angelo; CITERIO, Giuseppe. Acute traumatic brain injury in frail patients: the next pandemic. **Current opinion in critical care**, v. 28, n. 2, p. 166-175, 2022.

BEARD, Kryshawna; MEANEY, David F.; ISSADORE, David. Clinical applications of extracellular vesicles in the diagnosis and treatment of traumatic brain injury. **Journal of neurotrauma**, v. 37, n. 19, p. 2045-2056, 2020.

BRAZINOVA, Alexandra, *et al*. Epidemiology of traumatic brain injury in Europe: a living systematic review. **Journal of neurotrauma**, v. 38, n. 10, p. 1411-1440, 2021.

DE GUZMAN, Earl; AMENT, Andrea. Neurobehavioral management of traumatic brain injury in the critical care setting: an update. **Critical care clinics**, v. 33, n. 3, p. 423-440, 2017.

DENNIS, Emily L., *et al*. ENIGMA brain injury: Framework, challenges, and opportunities. **Human brain mapping**, v. 43, n. 1, p. 149-166, 2022.

GINER, J., *et al*. Traumatic brain injury in the new millennium: new population and new management. **Neurología (English Edition)**, v. 37, n. 5, p. 383-389, 2022.

HAARBAUER-KRUPA, Juliet, *et al*. Epidemiology of chronic effects of traumatic brain injury. **Journal of neurotrauma**, v. 38, n. 23, p. 3235-3247, 2021.

JINADASA, Sayuri; BOONE, M. Dustin. Controversies in the management of traumatic brain injury. **Anesthesiology clinics**, v. 34, n. 3, p. 557-575, 2016.

KHELLAF, Abdelhakim; KHAN, Danyal Zaman; HELMY, Adel. Recent advances in traumatic brain injury. **Journal of neurology**, v. 266, n. 11, p. 2878-2889, 2019.

LOGGINI, Andrea, *et al.* The role of amantadine in cognitive recovery early after traumatic brain injury: a systematic review. **Clinical Neurology and Neurosurgery,** v. 194, p. 105815, 2020.

MCGINN, Melissa J.; POVLISHOCK, John T. Pathophysiology of traumatic brain injury. **Neurosurgery Clinics**, v. 27, n. 4, p. 397-407, 2016.

MOLLAYEVA, Tatyana; MOLLAYEVA, Shirin; COLANTONIO, Angela. Traumatic brain injury: sex, gender and intersecting vulnerabilities. **Nature Reviews Neurology**, v. 14, n. 12, p. 711-722, 2018.

PUGH, Mary Jo, *et al*. Phenotyping the spectrum of traumatic brain injury: a review and pathway to standardization. **Journal of neurotrauma**, v. 38, n. 23, p. 3222-3234, 2021.

ROLDÁN, María; KYRIACOU, Panayiotis A. Near-infrared spectroscopy (NIRS) in traumatic brain injury (TBI). **Sensors**, v. 21, n. 5, p. 1586, 2021.

SAVITSKY, B., et al. Traumatic brain injury: it is all about definition. Brain injury, v. 30, n. 10, p. 1194-1200, 2016.

SEABURY, Seth A., *et al*. Assessment of follow-up care after emergency department presentation for mild traumatic brain injury and concussion: results from the TRACK-TBI study. **JAMA network open**, v. 1, n. 1, p. e180210-e180210, 2018.

TOCCALINO, Danielle; COLANTONIO, Angela; CHAN, Vincy. Update on the epidemiology of work-related traumatic brain injury: a systematic review and meta-analysis. **Occupational and environmental medicine**, v. 78, n. 10, p. 769-776, 2021.

WANG, Kevin K., *et al*. An update on diagnostic and prognostic biomarkers for traumatic brain injury. **Expert review of molecular diagnostics**, v. 18, n. 2, p. 165-180, 2018.

WILDE, Elisabeth A., *et al.* A framework to advance biomarker development in the diagnosis, outcome prediction, and treatment of traumatic brain injury. **Journal of neurotrauma**, v. 39, n. 7-8, p. 436-457, 2022.

WILLIAMS, W. Huw, *et al.* Traumatic brain injury: a potential cause of violent crime?. **The Lancet Psychiatry**, v. 5, n. 10, p. 836-844, 2018.

YAN, Amy, *et al*. Clinical Management in Traumatic Brain Injury. **Biomedicines**, v. 12, n. 4, p. 781, 2024.

Chapter 24

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Burns are skin injuries caused by direct or indirect contact with extreme temperatures, posing a significant public health challenge. In Brazil, approximately 1 million people suffer from burns annually, with the Unified Health System (SUS) spending around 55 million reais per year on treating these patients. This results in about 100,000 hospital visits and up to 2,500 annual deaths, significantly affecting the health and quality of life of those impacted. The depth and extent of tissue damage are fundamental classifications that directly influence clinical management and patient prognosis. In the context of

burns, the severity and complications associated with these injuries present a public health challenge, although most cases are preventable. Burns can result from direct or indirect heat action on organic tissues, causing trauma and compromising tissue integrity. They can be classified according to their origin into chemical and physical burns. Chemical burns are mainly caused by acidic and basic substances, while physical burns are associated with electricity, radiation, and extreme temperatures (Giordani *et al*., 2016).

The consequences of burns go beyond localized skin damage, potentially triggering severe systemic complications such as sepsis, hemodynamic instability, electrolyte imbalances, and shock. Additionally, they compromise patients' psychological and emotional integrity (Morais *et al*., 2022). Other complications include respiratory, renal, and metabolic imbalances. Fluid replacement is crucial to maintain vital organ function and preserve tissue perfusion, preventing hypovolemia (Callou *et al*., 2023).

The therapeutic approach to burns includes traditional techniques, such as the use of silver sulfadiazine, and recent innovations, such as the use of Nile tilapia skin. The latter is recognized for its histological properties similar to human skin and its effectiveness in treating severe skin injuries. Case studies have also shown that hyaluronic acid, when applied to lesions and wounds, retains water and creates a conducive environment for collagen and elastin formation, highlighting the importance of these innovations in clinical management (Dos Santos *et al*, 2022).

EPIDEMIOLOGY

Burn injuries are considered complex traumas due to their economic and social repercussions, presenting a morbidity and mortality rate affecting approximately 1 million people worldwide. In Brazil, this type of trauma directly impacts public health costs, with an average of 100,000 Brazilians hospitalized annually due to burns.

According to epidemiological data, only 10% of burn victims seek hospital care, with approximately 2,500 dying directly or indirectly from their injuries. Most patients are treated in emergency centers, and it is estimated that about 40,000 are hospitalized in severe condition (Giordani *et al*., 2016).

Most accidents occur in domestic settings, involving mainly adult males, children and adolescents under 15 years old, and the elderly. Burns are the second leading cause of trauma-related deaths in children up to 4 years old and the third in older age groups. In the pediatric and elderly populations, the home environment is the most prone to burn accidents, while for adults, these accidents are more prevalent in the workplace (Rocha *et al*., 2020).

The injuries are predominantly caused by scalding with hot liquids in children. In adolescents and adults, the main cause is related to the use of flammable liquids, commonly alcohol. Other frequent causes include exposure to fire, boiling water, and contact with heated objects (Giordani *et al*., 2016).

DIAGNOSIS

Diagnosing burns requires a detailed evaluation of the burn's degree, the Burn Surface Area (BSA), the presence of airway injury, and psychobiological needs, such as oxygenation, hydration, mucocutaneous integrity, elimination, and thermal, vascular, and electrolyte regulation, in addition to pain perception (Sousa *et al.*, 2021). Identifying the etiology of the burn and conducting a specific psychosocial assessment for the severely burned patient are crucial for effective and longitudinal therapy (Morais *et al.*, 2022).

The BSA is assessed to determine the burn extent using three main methods:

- Rule of Nines: Divides the body into segments, assigning specific percentages. In adults, the head and neck represent 9%, each arm 9%, each leg 18%, anterior trunk 18%, posterior trunk 18%, and genital area 1%. In children, the head represents 21% and each leg 12%.
- Palm Method: The patient's palm (including fingers) represents approximately 1% of the BSA.
- Lund-Browder Chart: More accurate for children, adjusts the percentages according to age.

Patient management is directed according to the degree of involvement, making early and detailed assessment necessary for better assistance and achieving a more favorable prognosis and better quality of life. An example is debridement, which, when performed timely, helps prevent sepsis by controlling systemic inflammation and aiding in healing (Vieira *et al.*, 2024).

Burn patients may present cardiovascular, respiratory, and renal dysfunctions and are at greater risk for chronic inflammation, shock, and sepsis (Callou *et al.*, 2023). Respiratory manifestations commonly include dyspnea, which can be caused by airway injuries or smoke inhalation, potentially leading to respiratory failure and, eventually, death. Symptoms such as stridor, soot in the sputum, tearing, wheezing, and productive cough are also common (Sousa *et al.*, 2021).

According to De Souza *et al.* (2019), seven major problems are evident in burn victims, which fit into symptomatology and complications: skin lesions, infection, pain, fluid alterations, edema formation, intracranial bleeding, and changes in body and emotional image. The pain clinical picture of these patients varies according to the burn degree. First- and second-degree burns are generally more painful due to less destruction of nerve endings. In contrast, third-degree burns can be less painful or even painless due to the complete destruction of nerve endings (Sousa *et al.*, 2021).

TREATMENT

Burns are serious injuries that require intensive and specialized care to minimize complications and promote proper recovery. When burns are more severe, they present an even greater challenge in clinical practice due to potential complications such as infections and disabling scarring. Appropriate treatment not only involves immediate healing but also the prevention of infections and functional restoration of tissues, highlighting the importance of proper injury management (Rocha *et al*., 2020). The good prognosis and quality of life of patients are directly linked to the training of healthcare professionals involved, who must be trained and updated to promote effective management and ensure positive outcomes (Vieira *et al*., 2024).

Burn injuries are classified according to depth:

- First Degree: Limited to the epidermis, presenting erythema, pain, and absence of blistering.
- Superficial Second Degree: Affect the epidermis and superficial dermis, associated with pain, redness, blisters, and the possibility of mild scarring.
- Deep Second Degree: Affect the reticular dermis, causing intense pain and complete loss of the dermis, resulting in fibrous scar tissue.
- Third Degree: Affect the entire dermis and subcutaneous tissue, being painless due to the destruction of nerve endings.
- Fourth Degree: Deep injuries that extend through all tissues, including bones, tendons, and muscles, being potentially fatal and highly susceptible to infections (De Souza *et al*., 2019).

Most burns occur in domestic or work environments due to the lack of proper equipment or safety measures. Anyone can be affected, although the elderly and children are more vulnerable and have a higher incidence of burns. This requires special and individualized care, ranging from outpatient care to treatment in Intensive Care Units (ICUs) for highly complex cases (Rocha *et al*., 2020).

The treatment of burn patients involves a multidisciplinary team, including plastic surgeons, emergency physicians, dermatologists, nurses, occupational therapists, and psychologists. The psychologist plays a crucial role in helping overcome the traumatic experience and aligning expectations regarding the therapies used, being essential for a good clinical outcome (Vieira *et al*., 2024).

Burn patients suffer significant emotional impacts due to physical and functional sequelae, as well as the painful process that influences recovery. Therefore, it is crucial to provide, in addition to physical care, emotional support. The actions of healthcare professionals should include detailed explanations about the stages of treatment and support for accepting changes and possible sequelae resulting from the trauma (Sousa *et al*., 2021).

Initial therapy includes hemodynamic stabilization and the prevention of vascular complications, following the "ABCDE" trauma protocol. After this stage, the body area affected by burns and their extent is estimated using the Rule of Nines (Callou *et al.*, 2023). Next, the patient's hydrostatic stabilization is performed following the Parkland formula, and then the focus is directed to the wound. If there is necrotic tissue, surgical debridement becomes essential for its removal, preparing the injury for proper healing. Local wound hygiene is then carried out, and dressings with healing and antimicrobial properties are applied (Dos Santos *et al.*, 2022).

Interventions may include the use of hydrocolloid and alginate dressings, which promote healing and reduce the risk of infections. Additionally, topical therapies with antiseptic agents prevent secondary infections and promote healthy tissue regeneration (Rocha *et al.*, 2020).

1% silver sulfadiazine remains a cornerstone in the initial treatment of third-degree burns due to its broad antimicrobial properties and its ability to reduce bacterial load in the wound bed. However, these dressings require frequent changes, increasing patient discomfort and associated costs, making them less accessible and more bothersome due to the pain caused during cleaning and dressing changes (Sousa *et al.*, 2021).

Recent studies have introduced an innovative approach to burn treatment with the application of tilapia skin. This technique has shown substantial advantages in the healing process and reducing discomfort associated with pain. Research on the use of stem cells has also shown high potential in the regeneration of affected tissues and improvement of dermal function in more severe cases (Callou *et al.*, 2023).

Despite advances, burn treatment faces significant challenges due to the high propensity for infections, healing difficulties, and the need for multiple surgical interventions. Strategies to overcome these obstacles include the appropriate use of antimicrobial agents according to resistance protocols, aiming to minimize the development of resistant bacteria (Vieira *et al.*, 2024). To promote effective tissue regeneration, the development and application of advanced skin graft techniques, such as cultured skin grafts, are fundamental. Additionally, it is essential to implement multidisciplinary protocols for pain management, incorporating pharmacological and non-pharmacological therapies to improve patient comfort during treatment (De Souza *et al.*, 2019).

REFERENCES

CALLOU, Pedro Henrique Cardoso, *et al.* Avaliação e Abordagem Inicial ao Paciente Grande Queimado no Departamento de Emergência: Uma Revisão Integrativa da Literatura. **Revista de psicologia**, v. 17, n. 66, p. 155-170, 2023.

DE SOUZA, Flávia dos Santos Lugão; DOS SANTOS, Maycown Junior; VALLE, Norma Sueli Braga; DE SOUZA, Isabel Maria. ABORDAGEM DE ENFERMAGEM AO PACIENTE VÍTIMA DE QUEIMADURAS: UMA REVISÃO INTEGRATIVA. **Brazilian Journal of Surgery & Clinical Research**, v. 27, n. 2, 2019.

DOS SANTOS, Michelle Danoski; LAVALL, Eliane; LOHMANN, Paula Michele; BAIOCCO, Graziella Gasparotto. Treatment of injuries caused by burns: an integrative review. **Research, Society and Development**, v. 11, n. 7, p. e26011729391-e26011729391, 2022.

GIORDANI, Annecy Tojeiro; SONOBE, Helena Megumi Sonobe; GUARINI, Gabriele; STADLER, Debora Viviane. Complicações em pacientes queimados: Revisão Integrativa. **Revista Gestão & Saúde**, v. 7, n. 2, p. ág. 535-548, 2016.

MORAIS, Maria Eduarda Ferreira Felga, *et al*. Abordagem global do paciente queimado: uma revisão de literatura. **Revista Eletrônica Acervo Médico**, v. 8, p. e10155-e10155, 2022.

ROCHA, Nathalia Menezes, *et al*. Atendimento inicial às vítimas de queimaduras: uma revisão integrativa. **Caderno de Graduação-Ciências Biológicas e da Saúde-UNIT-ALAGOAS**, v. 6, n. 1, p. 11-11, 2020.

SOUSA, Yara dos Santos; DOS SANTOS, Luana Araujo; ANDRADE, Bianca Gonçalves de; ARAÚJO, Andrey Hudson Interaminense Mendes de. Assistência de enfermagem à vítima de queimaduras: uma revisão da literatura. **Revista Eletrônica Acervo Enfermagem**, v. 12, p. e7770-e7770, 2021.

VIEIRA, Iana Carneiro, *et al*. Manejo Terapêutico do Paciente Queimado: Revisão de Literatura. **Brazilian Journal of Implantology and Health Sciences**, v. 6, n. 1, p. 1698-1715, 2024.

Chapter 25

STEVENS-JOHNSON SYNDROME

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CHAPTER 25

STEVENS-JOHNSON SYNDROME

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Stevens-Johnson Syndrome (SJS) is a severe, potentially fatal delayed hypersensitivity reaction affecting the skin. This condition can be triggered by various drugs, especially anticonvulsants, antibiotics, and anti-inflammatory drugs. Besides pharmacological causes, infections by certain microorganisms like viruses and bacteria, or the presence of some neoplasms, can also trigger the disease. SJS has a high mortality rate

in Brazil, ranging from 20% to 25%. The annual incidence is 1.2 to 6 cases per million inhabitants, being more prevalent in adult men (Vieira *et al.*, 2021).

In the prodromal period of SJS, nonspecific symptoms include fever, conjunctival itching, paresthesia, sensitivity to touch, and a burning sensation on the skin. This is followed by the abrupt onset of skin erythema, which can evolve from macules to papules, blisters, confluent erythema, vesicles, or urticaria plaques, usually without itching. Lesions are most common on the face, neck, chest, and mucous membranes. Treatment of SJS requires the immediate identification and suspension of the triggering agent. Early recognition of clinical signs and detection of the etiological agent are crucial for a positive prognosis. Efficient diagnosis, based on clinical signs and biopsy when necessary, is essential for patient recovery (Campos; Cintra and Ximenes, 2023).

Systemic treatment options are still limited and not always effective (Dourado; Ribeiro, 2023). SJS represents a public health challenge due to the difficulty of early diagnosis, indiscriminate use of medications by the population, complex management of severe complications, and the scarcity of specific screening tests (Leite *et al.*, 2024). Recently, diagnostic trends have focused on the use of predictive biomarkers to identify patients predisposed to adverse drug reactions. Additionally, research on the disease's pathophysiology is increasing to identify more specific therapeutic targets (Ribeiro; Ribeiro and Benito, 2017).

Proper treatment is vital for managing patients, relieving symptoms, and preventing infections. This includes topical treatment, such as creams and ointments, and systemic treatment involving corticosteroids, analgesics, immunoglobulins, cyclosporins, and antibiotics in case of sepsis (Campos; Cintra and Ximenes, 2023). Treatment should be personalized and often performed in Intensive Care Units (Dourado; Ribeiro, 2023). The complexity of Stevens-Johnson Syndrome represents a significant public health threat, highlighting the relevance of studies to improve clinical approaches and outcomes for affected patients (Campos; Cintra and Ximenes, 2023).

EPIDEMIOLOGY

The incidence of SJS increases with age, being more prevalent in adult men aged 20 to 53 years, although it can affect all age groups (Vieira *et al.*, 2021). Women, however, are more prone to experiencing adverse reactions due to differences in body weight, hormonal variations, more frequent medical consultations, and greater adherence to medical prescriptions (Dewi, 2019).

Various predisposing factors influence the incidence of these conditions, such as concomitant medical conditions, use of multiple medications, genetic predisposition, and immunosuppression. For instance, patients with HIV have an increased incidence up to 1000 times compared to the general population, with a rate of 1 case per 1,000 patients per year. Other factors include the presence of cancer and concurrent use of radiotherapy and anticonvulsants (Dewi, 2019).

Geographically, 90% of SJS cases involve hemorrhagic and painful mucosal involvement, especially in the oral, ocular, and genital mucosa. The location and extent of lesions vary among individuals, being more frequent in conjunctival, urethral, and oropharyngeal areas (Vieira *et al.*, 2021). Lesions include macules, papules, blisters, urticaria plaques, confluent erythema, and papules, which may have a purpuric, necrotic, or vesicular center, coalescing and displaying a positive Nikolsky sign (Ribeiro; Ribeiro and Benito, 2017).

SJS is mainly related to drug use due to delayed hypersensitivity reactions to certain substances in medications. Risk factors that increase this prevalence include infections, immunosuppressive disorders, and certain specific types of human leukocyte antigens. Additionally, multiple comorbidities, medication use, and diseases that activate the immune system are predisposing factors for developing SJS (Vieira *et al.*, 2021).

DIAGNOSIS

Early diagnosis of SJS and Toxic Epidermal Necrolysis (TEN) is challenging since, in their early stages, these dermatological conditions resemble other skin diseases. Due to the high mortality rate, a rapid diagnosis is crucial to improve the patient's prognosis (Caminha *et al.*, 2021).

SJS/TEN generally begins one to three weeks after contact with the etiological agent. In the initial stage, symptoms are nonspecific, including general malaise, fever (39-40°C), anorexia, rhinorrhea, asthenia, odynophagia, headache, myalgia, arthralgia, conjunctival itching, paresthesia, sensitivity to touch, and a burning sensation on the skin. These symptoms vary in intensity and duration, persisting for approximately one week.

The most characteristic sign of SJS/TEN is skin erythema, which appears abruptly as irregular, confluent erythematopurpuric macules with a "target" appearance. As the disease progresses, papular lesions and flaccid grayish blisters develop (Martínez-Cabriales; Gómez-Flores and Ocampo-Candiani, 2015). The Nikolsky sign, where superficial friction of the skin causes epidermal detachment, may be present and indicates the separation of the epidermis (Dourado; Ribeiro, 2023).

Lesions start on the trunk and later affect the neck, face, and upper limbs bilaterally and symmetrically (Martínez-Cabriales; Gómez-Flores and Ocampo-Candiani, 2015). They can occur anywhere but are most common on the face, neck, and chest (Dourado; Ribeiro, 2023). The extent of lesions is assessed based on the total number of blisters and areas positive for the Nikolsky sign. They are classified as follows (Sacoto, 2023):

- Stevens-Johnson Syndrome: Lesion on less than 10% of the body surface.
- Overlap between SJS and TEN: Lesion on 10-30% of the body surface.
- Toxic Epidermal Necrolysis: Lesion on more than 30% of the body surface.

Mucosal involvement occurs in 90% of patients and can be an indicator of progression from SJS to TEN (Martínez-Cabriales; Gómez-Flores and Ocampo-Candiani, 2015). Mucosal lesions, characterized by erosion and desquamation, affect the conjunctival, oropharyngeal, nasal, esophageal, urethral, anal, vaginal, and perineal mucosa (Vieira et al., 2021). The lesions are painful and can cause complications such as urinary retention, blepharitis, conjunctival hyperemia, and purulent conjunctivitis (Vieira *et al.*, 2021).

As SJS/TEN progresses, complications arise due to the involvement of the respiratory, cardiovascular, gastrointestinal, and renal systems, with a mortality rate of around 70% (Sacoto, 2023). The lack of epidermal protection increases susceptibility to sepsis, the main cause of death in these patients (Martínez-Cabriales; Gómez-Flores and Ocampo-Candiani, 2015). Nephrotoxic cytokines involved in SJS/TEN, along with hypovolemia and decreased cardiac output, can cause kidney injury, such as electrolyte imbalances, prerenal azotemia, tubular necrosis, and acute renal failure. Lung involvement can result in bronchiolitis obliterans or diffuse interstitial pneumonitis (Martínez-Cabriales; Gómez-Flores and Ocampo-Candiani, 2015).

Diagnosing SJS is challenging due to its clinical similarity to other skin diseases in the early stages but is more beneficial when performed quickly (Caminha *et al.*, 2021). The diagnosis is based on clinical history and physical examination, with cutaneous and mucosal lesions characterized by erosion and desquamation, mainly in the oral, ocular, and genital mucosa. In 90% of cases, there is hemorrhagic and very painful involvement, affecting less than 10% of the body surface (Vieira *et al.*, 2021).

The initial evaluation includes checking vital signs, a complete blood count, arterial blood gas analysis, renal and liver function, C-reactive protein, plasma protein electrophoresis, and blood glucose. Skin biopsy for histopathological study, which reveals minimal inflammatory cell infiltrate with a predominance of CD4+ T lymphocytes, apoptotic keratinocytes, and epidermal detachment, is the only specific test (Dourado; Ribeiro, 2023). Laboratory and imaging tests are important to assess the patient's current state and perform the SCORTEN, a test used to determine the patient's prognosis (Torres; Olmos, 2013).

Differential diagnosis includes diseases causing cutaneous lesions, such as linear IgA dermatosis, bullous pemphigoid, and staphylococcal scalded skin syndrome. Histopathological study, direct immunofluorescence, serum antibody determination, and clinical history help differentiate (Roujeau, 2017). Erythema multiforme is also a differential, with a different evolution, starting with lesions on the backs of the hands and symmetrical involvement (Roujeau, 2017).

TREATMENT

The treatment of SJS is primarily based on identifying and suspending the triggering agent. Subsequently, it is crucial to choose a pharmacological therapy according to the severity of the disease and the patient's clinical conditions, individually (Campos; Cintra

and Ximenes, 2023). There are several systemic treatment options. For systemic treatment, drugs like cyclosporine, intravenous immunoglobulin (IVIG), corticosteroids, and tumor necrosis factor-alpha (TNF-α) inhibitors are used (Sacoto, 2023).

Corticosteroids are effective in treating SJS and TEN, especially in severe cases, when administered early, in pulse regimen, or in selected subgroups (Campos; Cintra; Ximenes, 2023). However, the use of corticosteroids in TEN remains controversial due to increased complications and mortality in some studies. Early, short-duration administration in moderate doses (prednisone 1 to 2 mg/kg for 3 to 5 days) may be beneficial, although a more recent review has not confirmed this effect (Estrella-Alonso *et al.*, 2017).

Cyclosporines have shown beneficial results in mortality, but studies are limited due to the small number of participants. The recommended doses are 4 mg/kg/day, orally, divided into two doses, lasting no more than four weeks. Cyclosporine is well tolerated in most patients and can stop disease progression and initiate reepithelialization 2 to 5 days after starting treatment (Estrella-Alonso *et al.,* 2017).

TNF-α inhibitors, such as etanercept and infliximab, have shown benefits in a small number of cases, but their effectiveness has yet to be demonstrated due to a lack of controlled studies (Estrella-Alonso *et al.*, 2017). Thalidomide, another TNF-α inhibitor, is not recommended due to significant teratogenic risk and lack of evidence of effectiveness (Roujeau, 2017).

Plasmapheresis can be used to remove drugs, their metabolites, and cytotoxic mediators from the blood. Although it has demonstrated beneficial effects in some studies, it is generally used in combination with other treatments, making it difficult to assess its isolated effectiveness (Estrella-Alonso *et al.*, 2017).

There are also topical treatment options, such as creams, lotions, and ointments, which can relieve symptoms, reduce inflammation, decrease the risk of infections, speed up recovery, and prevent serious complications. Petrolatum gauze dressings and silver biosynthetic dressings are also used to cover lesions, preserve granulation tissue, and prevent infections (Ximenes *et al.*, 2023).

Supportive measures are essential for treating SJS and TEN. It is necessary to keep the patient well-nourished and hydrated, maintain hemodynamic balance, and use antibiotic therapy when necessary to prevent secondary infections (Campos; Cintra; Ximenes, 2023). Patients with severe forms of the disease should be transferred to specialized units to prevent life-threatening complications. Management is multidisciplinary and includes multiorgan care, early diagnosis, and cessation of the offending medication (Sacoto, 2023). Psychological and emotional support is also important due to the high traumatic degree of the disease (Ximenes *et al.*, 2023).

Oral, genital, and cutaneous erosions require antiseptic treatment. Ocular lesions should be managed by a specialist, using artificial tears and antibiotic eye drops without corticosteroids. Individual lesions usually heal within 1 to 2 weeks unless secondary

infection occurs. Most patients recover without sequelae, although mucosal lesions can cause late complications, such as bleeding and narrowing of affected sites. Patients should avoid future exposure to the SJS-causing agent (Roujeau, 2017).

REFERENCES

CAMINHA, Irla Carvalho Chaves, *et al.* Necrólise epidérmica tóxica/síndrome de stevens johnson: como o diagnóstico precoce pode impactar no prognóstico. **Revista Científica Multidisciplinar**, v. 2, n. 9, p. e29747-e29747, 2021.

CAMPOS, Sabryna Silveira; CINTRA, Bruno Barreto; XIMENES, Renata Maria Visniewski. Intervenções terapêuticas para o tratamento sistêmico da Síndrome de Stevens-Johnson (SSJ) e Necrólise Epidérmica Tóxica (NET): Uma revisão integrativa. **Research, Society and Development**, v. 12, n. 11, p. e71121143488-e71121143488, 2023.

DEWI, Cinthia Christina. Tinjauan atas Stevens-Johnson Syndrome dan Toxic Epidermal Necrolysis. **Cermin Dunia Kedokteran**, v. 46, n. 7, p. 55-59, 2019.

DOURADO, Eduardo Souza; RIBEIRO, Rebecca Heidrich Thoen. SÍNDROME DE STEVENS-JOHNSON: UMA REVISÃO BIBLIOGRÁFICA. **Revista Científica Multidisciplinar**, v. 4, n. 6, p. e463339-e463339, 2023.

ESTRELLA-ALONSO, Alfonso, et al. Necrolisis epidérmica tóxica: un paradigma de enfermedad crítica. **Revista Brasileira de Terapia Intensiva**, v. 29, p. 499-508, 2017.

LEITE, Letícia dos Anjos; PAIVA, Lívia Vitória de Carvalho; MIRANDA, Thais Serralheiro; DOS SANTOS Anna Catarina Moreira. SÍNDROME DE STEVEN JOHNSON: UMA REVISÃO ABRANGENTE DAS MANIFESTAÇÕES CLÍNICAS E TERAPÊUTICAS. **Revista Contemporânea**, v. 4, n. 4, p. e3889-e3889, 2024.

MARTÍNEZ-CABRIALES, Sylvia Aide; GÓMEZ-FLORES, Minerva; OCAMPO-CANDIANI, Jorge. Actualidades en farmacodermias severas: síndrome de Stevens-Johnson (SSJ) y necrólisis epidérmica tóxica (NET). **Gac Med Mex**, v. 151, n. 6, p. 777-87, 2015.

RIBEIRO, Anaira Gonçalves de Almeida; RIBEIRO, Maria Cristina; BENITO, Linconl Agudo Oliveira. Síndrome de Stevens-Johnson (SSJ) em adultos: revisão sistemática. **Universitas: Ciências da Saúde**, v. 15, n. 2, p. 117-125, 2017.

ROUJEAU, J.-C. Eritema multiforme. **EMC-Dermatología**, v. 51, n. 3, p. 1-9, 2017.

SACOTO, Gabriela Maribel Macancela. Necrólisis epidérmica tóxica. **Dominio de las Ciencias**, v. 9, n. 4, p. 330-346, 2023.

TORRES, Mauricio; OLMOS, Édgar. Reacciones medicamentosas severas Síndrome Stevens Johnson y síndrome DRESS. **Acta Médica Colombiana**, v. 38, n. 2, p. 76-82, 2013.

VIEIRA, Natália Abreu Silva, *et al.* Síndrome de Stevens-Johnson: revisão integrativa. **Revista Sustinere**, v. 9, n. 1, p. 96-107, 2021.

XIMENES, Renata Maria Visniewski; CINTRAET, Bruno Barreto Cintra; CAMPOS, Sabryna Silveira; GALINDO, Layanne Liege Domingos. Bases do tratamento tópico na Necrólise Epidérmica Tóxica e Síndrome de Stevens-Johnson: Uma revisão científica. **Research, Society and Development**, v. 12, n. 9, p. e12012943293-e12012943293, 2023.

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